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ETC: A Mechanistic Concept for Inorganic and Organic Chemistry**

By Michel Chanon* and Martin L. Tobe*

Dedicated to Professor Jacques Metzger on the occasion of his 60th birthday

The concept of electron transfer catalysis (ETC), or more specifically "Double Activation Induced by Single Electron Transfer" (DAISET) gives an opportunity to connect experimental facts never previously correlated. The first activation results from the transfer of an electron to (or from) a molecular species; the second activation results from the build-up of a reaction chain able to reproduce the species formed in the first step. The starting point of this review is the $S_{RN}1$ mechanism where principle and experimental diagnostic criteria are critically discussed. The thermal and photochemical exchange and substitution reactions of Pt^{IV} complexes are then reviewed together with the exchange reaction $[AuCl_4]^-/Cl^-$, reactions with Grignard reagents and other organometallic reagents, as well as the redox behavior of electronically excited organic compounds. Photochemical applications, including solar energy conversion are discussed. New aspects are also presented for the mechanistic problem "S_N2 reaction or SET process?" Moreover, the concept has significance for S_H2 reactions at metal centers, molecule-induced homolyses, reactions of complexes, as well as electrochemical processes.—Unless otherwise specified, only double activation (DAISET) processes will be discussed in this article.

1. Introduction

The subject of chain reactions is usually not considered as a whole but rather in relation to organic radical reactions and oxidations, polymerizations, gas phase chemistry, photochemistry, catalysis, *etc.* (cf. *e.g.* [1]). This dispersion presents serious drawbacks. In the present article we shall compare the mechanistic features of a special type of chain reaction whose study has, until now, developed completely independently in two apparently unrelated parts of chemistry; reactions at carbon, and reactions of transition metal complexes. All these reactions have been explained by single electron transfer (SET). Analysis of these reactions leads to the formulation of a concept which applies specifically to organic and inorganic exchange reactions but, in a wider sense, to some aspects of halogenations, isomerizations, eliminations, reductions, oxidations, polymerizations, transition-metal catalyzed reactions, sigmatropic rearrangements, and oxidative additions. The common feature of this class of reaction is the "DAISET" behavior: electron transfer to or from the substrate activates this toward association, dissociation or isomerization (first activation); the species thus created then enter into a catalytic cycle (second activation). An equivalent and simpler descriptor is therefore "Electron Transfer Catalysis" (ETC). The pervasiveness of this class of reaction leads one to expect a variety of applications, *e.g.* in photochemistry, in polymerizations, and in the conception of new chemical processes.

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[**] ETC: "*E*lectron *T*ransfer *C*atalysis"; DAISET: "*D*ouble *A*ctivation *I*nduced by *S*ingle *E*lectron *T*ransfer"; SET: "*S*ingle *E*lectron *T*ransfer".

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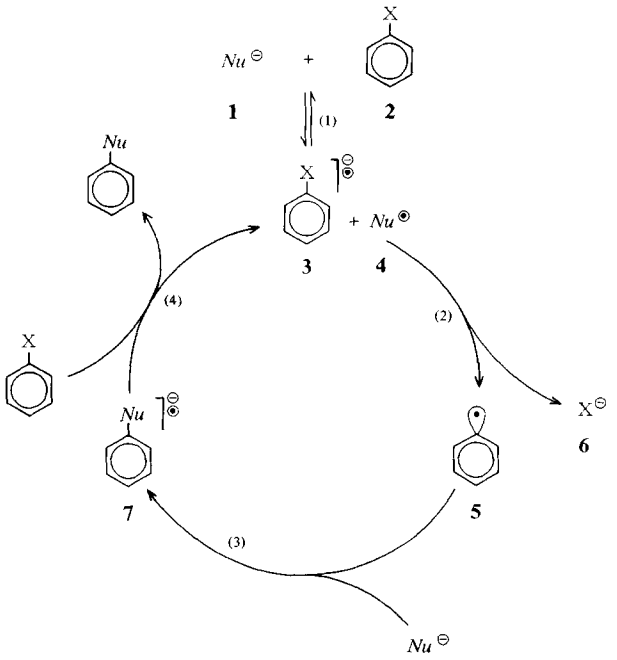
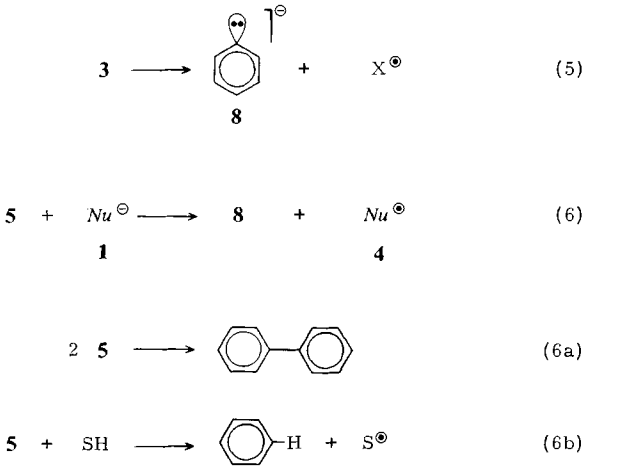
2. Principles of the ETC Concept for Substitution Reactions at Carbon

The mechanism we shall focus on now was proposed in 1966[2a–c]. It explained some very unexpected results of ambident alkylations and permitted the development of novel mild synthetic processes[2d]. *Bunnett* later extended it to substitution reactions of aromatic compounds, termed it $S_{RN}1$, and clearly showed its great potential in synthetic chemistry[3].

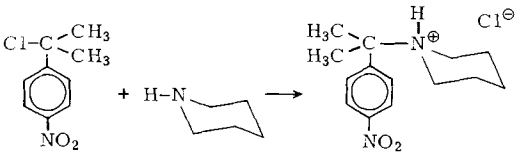


Termination



Scheme 1.

The ETC concept is illustrated in Scheme 1. The first activation occurs in step (1) with the transfer of an electron to the arene; thereby the quite unreactive C_{sp^2}—X bond is activated. The second activation results from the creation of a chain reaction whose active carrier is the radical anion **3**. The overall macroscopic result of this double activation is that reactions such as (7), usually thought to be highly improbable, become feasible under mild conditions[4]. Scheme 1 provides additional information.



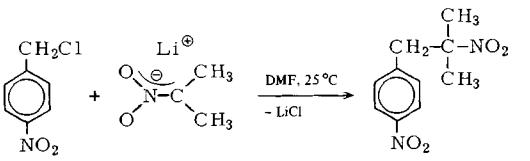
Waters was the first to propose a reaction such as the addition of the radical **5** to an anion **1** as long ago as 1942[5]; however, the first concrete evidence was provided much later by the ESR studies of *Russell*[6a]. This type of reaction is now widely accepted[6b]. The radical anion **7** must be more stable towards dissociation than **3**, otherwise it will decompose faster than electron transfer to the substrate **2**. Finally, the generation of any of the species **3**, **5**, or **7** in the medium by an appropriate reagent will provide entry to the chain propagation cycle.

3. Experimental Criteria Relating to the Assignment of the $S_{RN}1$ Mechanism

Since in the following sections we intend to compare apparently unconnected topics, it is important to enumerate the major pieces of experimental evidence for the involvement of an $S_{RN}1$ mechanism. This is particularly critical if it is noted that the overall stoichiometry of $S_{RN}1$ and S_N2 reactions are almost identical (products of termination reactions generally being present in trace amounts).

3.1. Failure to Follow a Simple Linear Free Energy Relationship

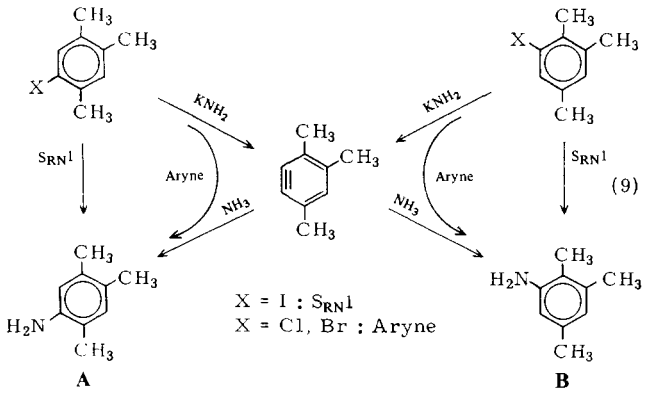
The starting point of the discovery of the $S_{RN}1$ mechanism was the unusual behavior of *p*-nitrobenzyl chloride which reacted with the ambident anion of 2-nitropropane to give a *C*-alkylated product in 92% yield[7].



Other *p*-substituted benzylic chlorides (CN, CF_3, $\overset{+}{N}(CH_3)_3Cl^-$, CH_3, Br) react with the anion mentioned to give exclusively the *O*-alkylated product. This result cannot be explained by σ parameters.

When *Bunnett et al.* discovered the $S_{RN}1$ mechanism his attention was drawn to analogous experimental evidence[8a]. On reacting 1,2,4-trimethylbenzenes with KNH_2 in ammonia, *i.e.* under conditions where the production of an aryne intermediate was expected, he observed an unexpected selectivity ratio **A/B** for the iodo compound.

Bunnett explained this result on the ground that iodated 1,2,4-trimethylbenzenes are able to react *via* an $S_{RN}1$ mechanism, whereas bromo and chloro derivatives do not.

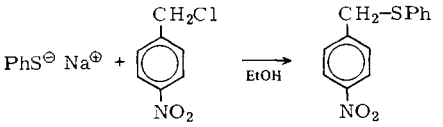


(9)

Many reactions which do not proceed according to this mechanism do not obey simple linear free energy relationships[8b]. Hence, this criterion may be a valuable preliminary indication, but is seldom a definite proof.

3.2. Detection of Radicals by ESR Studies

The proof that paramagnetic intermediates are involved in the $S_{RN}1$ mechanism was demonstrated by ESR studies[9a]. Reaction (8) carried out in dimethylformamide at $-50\,^{\circ}C$ reveals an unambiguous, albeit unresolved ESR signal of *ca.* 30 Gauss line width. Recently *Russell et al.*[10] were able to obtain fairly well resolved ESR spectra in reaction (10).



(10)

As a physical method very sensitive to trace amounts of material, ESR spectroscopy may strongly suggest the participation of an $S_{RN}1$ mechanism but cannot prove that this is the only one involved.

3.3. Abnormal Order of Leaving Groups

In the reaction of benzyl halides with the lithium salt of 2-nitropropane[9a], originally studied by *Kornblum et al.*, the rate of *O*-alkylation (normal S_N2 reaction) increases by a factor of 900 on proceeding from the chloride *via* the bromide to the iodide; in sharp contrast, the rate of *C*-alkylation only increases by a factor of 6[9a]. With aromatic substrates the usual order of reactivity for nucleophilic substitution is

$$ArylF \gg ArylCl \approx ArylBr \approx ArylI$$

which for the $S_{NR}1$ reaction becomes:

$$ArylI > ArylBr > ArylCl > ArylF$$

However, as already mentioned (Section 3.1) this criterion may be ambiguous: for example the aryne mechanism may also cause the "abnormal" order of leaving group abilities.

3.4. Chain-Interruption by Scavengers

If a scavenger able to trap one of the intermediates involved in the chain propagation step is added to the reaction mixture, the reaction is suppressed. This has been the most commonly used criterion to demonstrate that the $S_{RN}1$ mechanism actually operates. *Kornblum et al.* used *p*-dinitrobenzene as inhibitor of the *C*-alkylation[2a], and *Bunnett et al.* used tetraphenylhydrazine to scavenge the intermediates of the $S_{RN}1$ reaction[8a]. However, it must be kept in mind that a scavenger can compete with the other species present in the chain and may give negative results simply because it is not reactive enough. A chain mechanism for the reaction of oxygen with diborane was only proved when the highly reactive scavenger, galvinoxyl, became available[11] (cf. Section 6.4).

3.5. Photostimulation

$S_{RN}1$ reactions are usually greatly accelerated by irradiation. For example, the photochemically accelerated reaction between diethylphosphite and iodobenzene[12] in dimethyl sulfoxide was shown to occur with quantum yields of 50[14], and *Wade*[13] found even greater quantum yields for the photochemically induced substitution of *p*-nitrobenzyl halides. The catalytic function of the near UV is probably due to single electron transfer (SET) from the nucleophile to the substrate *via* an intermediate CT-complex[14]. This criterion is often used without precise measurement of quantum yields, and can provide misleading information; many reactions are photostimulated, and *inter alia Cornelisse* and *Havinga*[15] have reviewed arene substitutions. A feature of the photostimulated $S_{RN}1$ reaction is the high quantum yield. However, since the rate of a chain reaction is equal to the product of the chain length (chain length = chain propagation rate/chain termination rate) and the rate of formation of active species, one can readily imagine $S_{RN}1$ reactions that lead to quantum yields < 1. The necessary conditions are the association of a rather short chain with a very low primary quantum yield.

3.6. Racemization

Because of experimental problems, this criterion has seldom been used. It nevertheless played an important role in the development of the $S_{RN}1$ concept since it provided the first experimental evidence that the same nucleophile may react simultaneously *via* an SET process and an S_N2 reaction[16]. Whereas the SET process is characterized by racemization, the S_N2 mechanism leads to an inversion of configuration at the electrophilic center[17].

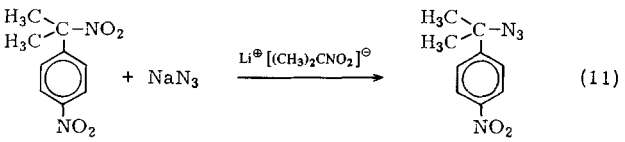
3.7. Formation of Typical Secondary Products

Since radicals play an important role in the $S_{RN}1$ mechanism, secondary products resulting from their dimerization or disproportionation should be observed. However, if the chain process is efficient the final products will be almost free of by-products. Dimerization products have neverthe-

less been reported[18] and, when present, give a valuable indication of the possible occurrence of an $S_{RN}1$ mechanism.

3.8. Activation by Catalytic Chain Initiation

The chain mechanism (Scheme 1) suggests that a catalytic amount of a reactive nucleophile might induce the reaction of a less reactive or even non-reactive nucleophile with an electrophilic center susceptible to $S_{RN}1$ reactivity. The role of the activator is to initiate the propagation cycle which continues by consuming the non-reactive nucleophile. The reaction of α-*p*-dinitrocumene and sodium azide provides a striking example of this phenomenon. These two compounds do not react at all within 48 h in the dark, but when the mixture is treated with the lithium salt of 2-nitropropane (1 : 2 : 0.1 molar ratio) a 97% yield of pure *p*-nitrocumyl azide is obtained in 3 h[19].



(11)

This criterion of catalytic chain initiation has been widely used in aromatic $S_{RN}1$ reactions where the added species ("solvated electron") may either be generated by an excess of alkali metals[20] or at the cathode[21,22].

3.9. Typical Electrochemical Processes

When the electron is generated electrochemically, deeper insight into the detailed mechanism is gained by use of cyclic voltammetry and polarography. By means of these methods considerable information about the fundamentals of the $S_{RN}1$ mechanism has been gained[21,22,300].

3.10. Kinetic Data

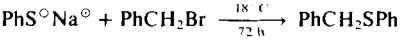
It is worth noting that kinetic rate laws have seldom if at all been used as a definite proof for the $S_{RN}1$ mechanism. The first reports by *Kornblum* interpreted the rate of *C*-alkylation by the approximation:

$$v = k[RX][Nu]$$

which does not, obviously, suggest a chain mechanism. According to *Shein*[23], the presently accepted classification of the reaction mechanisms of nucleophilic substitutions of arenes based on the reaction order, is inadequate. This lack of data may be partly understood since there are more elementary reactions than products[24]. However, some indications may be gained by kinetic measurements[25]. In any case, the application of kinetic simulations[26] to chain mechanisms in solution should help to clarify the effect of changes in the elementary steps on the overall kinetics.

3.11. Induced Polymerization of Styrene

An original and efficient way of showing that radical species are present in a solution is to use them to initiate a chain reaction. In this way, even if the amounts of radical are very small, a "chemical amplification" arises[27]. Using this principle, *Surzur et al.*[28] were able to demonstrate the presence of free radicals in the reaction (12).



(12)

This experiment, however, does not guarantee that a chain develops from the radical when styrene is no longer present.

3.12. Magnitude of Isotope Effects

In investigations of radical production from the interaction of closed-shell molecules, *Pryor et al.*[29] discovered an interesting test for distinguishing S_N2 reactions from SET mechanisms. Reactions of nucleophiles with peroxides can be divided, according to isotope effect, into two classes. If the rate constant for β-deuteration displays an inverse isotope effect (*i.e.* $k_H/k_D < 1$) then the mechanism is probably S_N2. In contrast, if $k_H/k_D > 1$, then the SET mechanism is preferred. Besides its practical importance, this test could provide deeper insights (Section 6.3) into the actual mechanistic competition between the S_N2 and SET within a given solvent cage ("magnetic isotope effect"[30]).

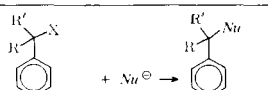
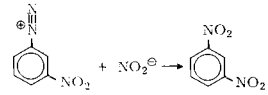
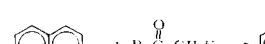
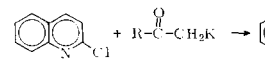
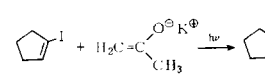
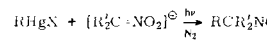
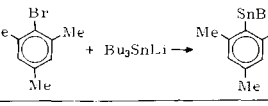
3.13. Replacement of Two Substituents without the Intermediate Formation of Monosubstitution Products

Several dihalobenzenes react photochemically with phenoxide ion to form disubstituted products without substantial formation of monosubstitution products as intermediates[31]. This result is consistent with the $S_{RN}1$ mechanism and constitutes powerful evidence for this reaction path.

3.14. Synergic Criteria

A chemist interested in the $S_{RN}1$ mechanism might well ask whether all thirteen criteria should be satisfied to prove the mechanism. Table 1 contains some information concerning the answer to this question: typical reactions have been collected, together with the experimental evidence required to prove an $S_{RN}1$ mechanism. No attempt has been made to be comprehensive. Table 1 shows that a single observation of photostimulation may be misleading (Section 3.5); observation of photostimulation and scavenging effects seems acceptable as a definite proof of an $S_{RN}1$ mechanism in exchange reactions[45,46] (cf. however, Section 6.1.2).

Table 1. Experimental evidence indicating an $S_{RN}1$ mechanism.

Reaction	Solvent [a]	Criterion No. [b]												
		1	2	3	4	5A 5B	6	7	8	9	10	11	12	13
	DMF	[32] [35]	[9a]	[9a]	[33a]	[34][13]	[13,17]		[36]			[28]		
PhX + $Nu^{\ominus}$ → PhNu + $X^{\ominus}$	NH_3 [8] DMSO [39]	[37]		[38]	[8]	[12][14]	[c]		[40,41]	[21] [22]				[31]
	[e] [25]				[25]			[25]			[25]			
	MeOH [14]		[42]		[18]	[18][d]		[18]						
	NH_3 [43]	[43]				[43]			[43]					
	NH_3 [45]					[44]		[44]	[44]					
	DMSO DMF [45]				[45]	[45]								
	THF [46]				[46]	[46]								

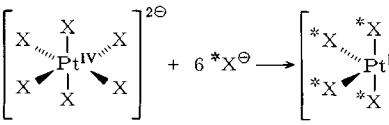
[a] Representative solvent. [b] The criteria are numbered as in the text; *e.g.* "4" corresponds to Section 3.4. 5A signifies: qualitative photostimulation; 5B signifies: determination of the quantum yield. [c] In this instance the stereochemistry is unimportant. [d] Weak effect. [e] Aqueous buffer solution.

4. ETC S in Octahedral Complexes[*]

4.1. Experimental Observation and Reexamination of the Mechanisms

To find the inorganic counterpart of the $S_{RN}1$ mechanism we must look for a reaction which fulfills most of the criteria given in Table 1. Table 2 summarizes the observations relating to reaction (13), X = Cl.

From a comparison of Tables 1 and 2 it follows that reaction (13) proceeds *via* an ETC mechanism (Scheme 2; the species and reaction steps are numbered as in Scheme 1).



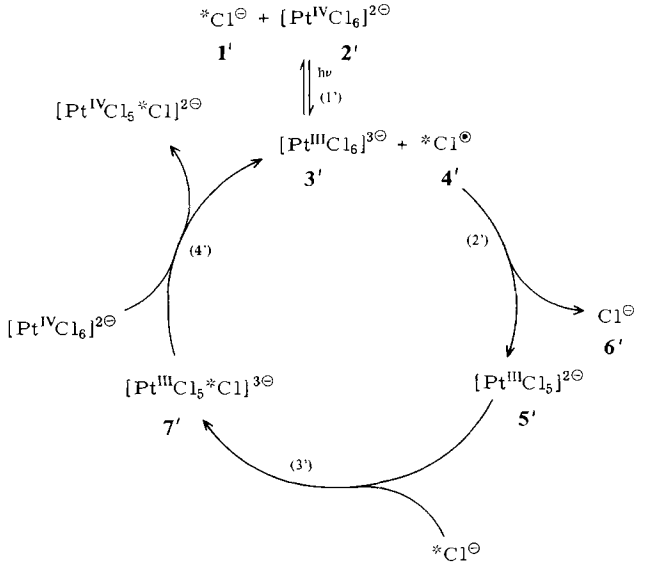
(13)

Table 2. Observations on reaction (13), X = Cl, a typical inorganic $S_{RN}1$ reaction (criteria no. 5A, 5B, see Table 1; cf. also Scheme 2).

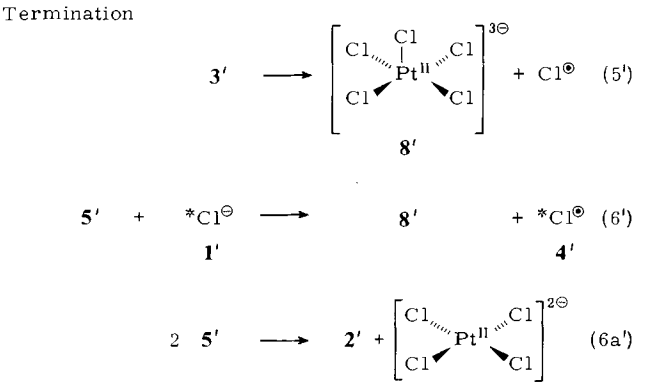
Observation	Method Criteria No.	Ref.
Aqueous solutions of K_2PtCl_6 (0.039 mol/L) in the dark in presence of $Cl^{\ominus}$ ions (0.0087 mol/L) at 25° exchanges 20% in 20 min in the dark. The same solution in diffuse day light exchanges 100% in the same time.	Kinetics with ^{36}Cl (5A)	[47a]
In the presence of hydroquinone or $K_3Fe(CN)_6$ the exchange no longer takes place.	Kinetics with ^{36}Cl (4)	[47a]
The rate of exchange in Pt^{IV} complexes depends upon the concentration of the substituting agent. These data have been interpreted as a redox process which sets up a chain mechanism. The equation $k_{obs} = k_1 \left[\frac{k_1}{k_2}\right]^{1/2} \left[\frac{Pt^{II}}{Pt^{IV}}\right]^{1/2} [Y]$ derived from the above mechanism is found to agree with the observed results.	Kinetics (10)	[48]
The $[PtCl_6]^{2-}$ /I exchange reaction is greatly accelerated by small amounts of thiosulfate or Fe^{II}.	Kinetics (8)	[49, 50]
The quantum yields of the exchange reaction $[(PtCl_6]^{2-}$ /Cl have been measured at various temperatures, pH values, and wavelengths and vary between 15 and 1000 [51]. The values depend on the square root of the light intensity and on the halide concentration [52].	Photochemistry (5B)	[51, 52]
The spectrum of the transient obtained during a flash photolysis study of $[PtCl_6]^{2-}$ [53] is virtually identical to that of the Pt^{III} species obtained by pulse radiolysis of $[PtCl_6]^{2-}$ [54].	Flash photolysis Pulse radiolysis (2)	[53–56]
The UV spectrum of *trans*-$[Pt(en)_2Cl_2]^{2+}$ changes considerably [57] on addition of excess Br or I . This was explained by the formation of a CT-complex. CT-complexes have been observed in typical $S_{RN}1$ reactions [14].		[57, 58]

[*] S signifies substitution.

This mechanism has never been considered before for this reaction. For sake of brevity we only represent the case where a radioactive chloride at the labile Pt^{II} complex is exchanged. It is clear however, that, depending on the relative rates of SET and substitution, several successive substitutions may occur before the last electron transfer occurs. This situation would exactly correspond to the reactivity of polyhaloarenes[31]. In 1954, *Taube et al.*[47a] proposed the mechanism in Scheme 3 for this kind of reaction,



Termination



Scheme 2. *Cl = ^{36}Cl.

Initiation

$$[Pt^{IV}Cl_6]^{2\ominus} \xrightarrow[\text{Photo-dissociation}]{h\nu} [Pt^{III}Cl_5]^{2\ominus} + Cl^{\odot} \quad (14)$$

Propagation

$$[Pt^{III}Cl_5]^{2\ominus} + {}^*Cl^{\ominus} \xrightarrow{\text{Exchange}} [Pt^{III}Cl_4{}^*Cl]^{2\ominus} + Cl^{\ominus} \quad (15)$$

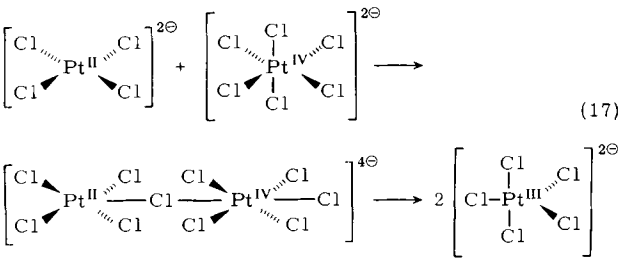
$$[Pt^{III}Cl_4{}^*Cl]^{2\ominus} + [Pt^{IV}Cl_6]^{2\ominus} \xrightarrow[\text{Inner Sphere}]{\text{SET}} [Pt^{IV}Cl_5{}^*Cl]^{2\ominus} + [Pt^{III}Cl_5]^{2\ominus} \quad (16)$$

Termination

$$2\,[Pt^{III}Cl_5]^{2\ominus} \xrightarrow[\text{tionation}]{\text{Dispropor-}} [Pt^{IV}Cl_6]^{2\ominus} + [Pt^{II}Cl_4]^{2\ominus}$$

Scheme 3. *Cl = ^{36}Cl.

discovered experimentally as early as 1832[59] and sporadically studied before 1954[60,61]: in the absence of experimental evidence the termination step was only tentatively suggested. Clearly, the mechanism (14)—(16) explained the catalytic action of reducing agents (including $[Pt^{II}Cl_4]^{2-}$) *via* an inner sphere redox mechanism (17).



Taube's mechanism departs from the $S_{RN}1$ type in one major point. At least in the Pt^{IV} complex, the presence of two chloride ions, one for the initiation step and the other for the substitution step, are required. As a consequence, *Taube*'s mechanism cannot be extended to organic substrates where an $S_{RN}1$ mechanism was discovered; on the other hand the $S_{RN}1$ mechanism perfectly (but see [47b]) explains the experimental data reported for inorganic substrates including the fact that $[Pt^{IV}(NH_3)_5I]^{3+}$ undergoes ligand exchange I^-/Br^-, catalyzed by $[Pt(NH_3)_4]^{2+}$[62]. In addition, the $S_{RN}1$ mechanism explains why a) conflicting rate laws were reported for this type of reaction[48,51], b) the addition of Ce^{IV} as quencher[64] may lead to equivocal results, and c) hydration products may be formed during the exchange[63c,65,66].

The $S_{RN}1$ mechanism is consistent with physical data obtained by flash photolysis[66–69] and pulse radiolysis[55,56,70,71] studies, and until now unconnected with the results of "classical" evidence. The isotopic exchange reaction of $[Pt^{IV}Br_6]^{2-}$[72,73] and the ligand exchange reactions $[Pt^{IV}Cl_6]^{2-}/Br^-$[63d] and $[Pt^{IV}Br_6]^{2-}/Cl^-$[63e], may be reinterpreted in the light of the $S_{RN}1$ mechanism.

Table 3 tentatively summarizes the insights that the present unification brings to organic and inorganic chemists.

4.2. Inspection of the Double Electron Transfer Mechanism

One point related to isotopic exchange catalyzed by Pt^{II} complexes deserves further comment.

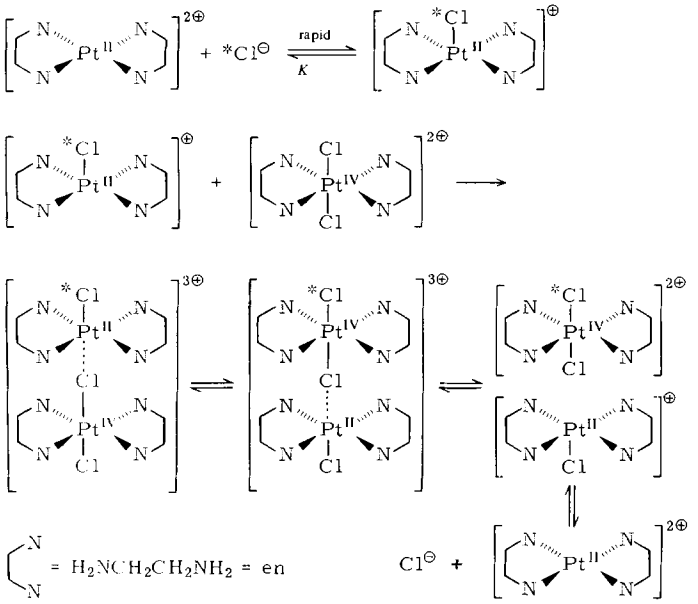
In 1958 *Basolo, Pearson et al.*[64a,83,84] proposed a mechanism to explain the catalytic activity of $[Pt^{II}(en)_2]^{2+}$ in chloride exchange in $[Pt^{IV}Cl_2(en)_2]^{2+}$ (Scheme 4). This, in the meantime, classic mechanism involves a "double electron transfer".

In a typical run, an aqueous solution of *trans*-$[Pt^{IV}(en)_2Cl_2]^{2+}$ (0.001 mol/L) in the presence of excess HCl (0.01 mol/L) and catalytic amounts of $[Pt^{II}(en)_2]^{2+}$ (0.0002 mol/L) kept at 25 °C in the dark exchanged chloride at a rate of 9.2×10^2 mol L^{-1} min^{-1}. Addition of 0.002 mol/L hydroquinone after one half-life did not measurably alter the exchange rate. (In [64a] it is not specified why

Table 3. New Insights provided by the unification of experimental results from inorganic and organic chemistry within the ETC concept.

Inorganic Chemistry	Organic Chemistry
The mechanism of isotopic exchange proposed for platinum complexes [47a] should be modified.	Flash photolysis and pulse radiolysis could provide more information on the ETC concept of organic substrates.
The chain mechanism $S_{RN}1$ may coexist with the double electron transfer mechanism [83] for some Pt^{IV} complexes. This proposition should also be checked for the other complexes displaying ETC behavior (Table 6).	Precise quantum yield determinations should be reexamined after the publication by *Stranks et al.* [80].
The electrochemistry of some inorganic complexes [74] should be reinvestigated taking into account the results obtained by *Savéant et al.* [21] and *Simonet-Lund et al.* [22].	Some exchange reactions could proceed *via* an $S_{RN}1$ mechanism.
Some aspects of reactivity linked to square planar complexes [75-77] should be considered keeping in mind the parallel between the activity of arenes and square planar complexes.	Some ETC reactions could start *via* an inner sphere SET. More generally the inner sphere outer sphere distinction [82] could profitably be introduced in the organic chemistry nomenclature.
The ETC concept could find other applications in the reactions of Pt^{IV} and Pt^{II} [78].	Oxidative ETC reactions should be more often considered as a possible mechanism (Section 5.2) and the experiments necessary to reject it conceived.
Reactions between paramagnetic inorganic complexes and generalized nucleophiles, according to step (3) should be carried out.	More attention should be paid to the experimental determination [143] of redox properties of excited states.
The ambident reactivity of some nucleophiles towards inorganic complexes [79] could sometimes parallel the behavior described by *Kornblum et al.* [2a, c, d].	The relation between standard potential proposed in 1978 [21b, c] is not an absolute necessity for the observation of ETC.
Inorganic photochemical reactions should be carefully considered in relation to the ETC mechanism.	Exploration of the reactivity of polyhalogeno alkanes and alkenes could be interesting within ETC. ETC reactions may occur in water.
	The treatment of general acid/base catalysis should, under certain conditions, include a SET term.
	ETC S, E, A, Re, Ra, Ox mechanisms should systematically be investigated as an efficient way to activate inert substrates.
	The photochemical reactivity of organic species in the presence of oxidizing and reducing agents should be systematically investigated.
	Molecular assisted homolysis (MAH) should be reexamined [252d] in relation to ETC (see Section 6.5.4).

the addition was carried out after one half-life rather than at the start.)

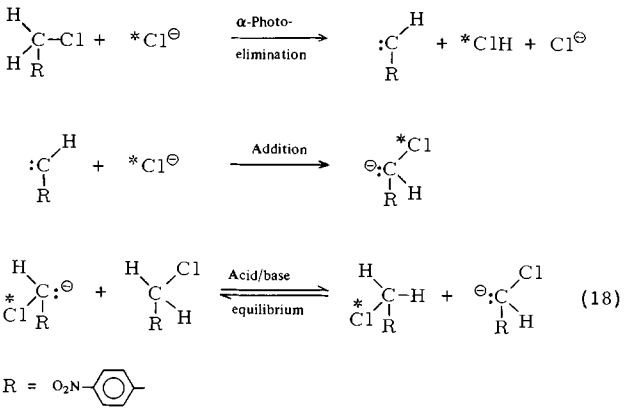


Scheme 4. *Cl = ^{36}Cl.

The two electron transfer mechanism has been the starting point for a large number of quantitative studies (cf. *e.g.* [86]).

Application of the mechanism (Scheme 4) to a supposed radioactive chloride exchange on a benzylic substrate is shown in Scheme 5.

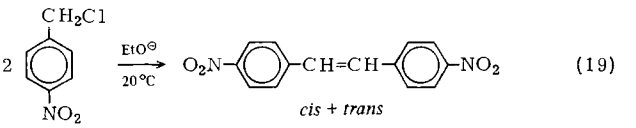
In this analogy, the carbene corresponds to a square planar Pt^{II} complex: to pass from an octahedral $[Pt^{IV}X_6]^{2-}$ to the planar $[Pt^{II}Cl_4]^{2-}$, a reductive elimination is required which is exactly equivalent to the α-elimination in the language of the organic chemist. In reaction (18) the "bridge" is formed by the H atom.



(18)

Scheme 5. *Cl = ^{36}Cl.

Some organic reactions originally thought to involve carbenes[87-89] have recently been reinterpreted by *Russell et al.*[10] in terms of an $S_{RN}1$ mechanism, *e.g.* reaction (19)[87].



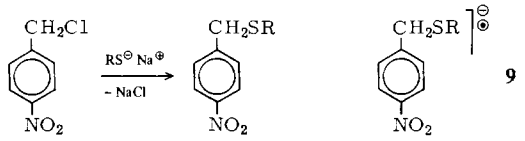
(19)

Before *Kornblum* proposed the chain mechanism he performed several experiments to reject the carbenoid hypothesis[90].

Recently, *Elding* and *Gustafson*[91,92] noticed that during chloride addition to *trans*-$[Pt^{IV}Cl_4(H_2O)_2]$ and to *trans*-$[Pt^{IV}(CN)_4Cl(H_2O)]^-$ in the presence of $[Pt^{II}Cl_4]^{2-}$ the primary reaction product was $[Pt^{IV}Cl_5(H_2O)]^-$. Furthermore, a discrepancy between the value of the equilibrium constant for the process

$$[Pt^{II}L_4]^{2\oplus} + X^{\ominus} \overset{K}{\rightleftharpoons} [PtL_4X]^{\oplus}$$

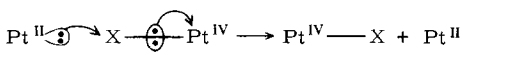
obtained from a kinetic analysis using the expression derived from the bridged mechanism and that estimated directly by spectrophotometry was found. To rationalize these findings the authors proposed that the thermal reaction begins with the formation of a dinuclear complex from the Pt^{IV} substrate complex and the simple Pt^{II} complex hydrated in the axial position is formed. In this mechanism, the implicit assumption is made that the bridged intermediate is sufficiently long-lived to undergo substitution and two electron transfer. The experimental results could, however, be interpretated completely differently according to the recent report of *Russell* on organic derivatives[45]. This author showed that a given nucleophile and electrophile may simultaneously undergo $S_{RN}1$- and S_N2-substitutions. The reaction of thiophenoxide or methanethiolate ion with *p*-nitrobenzyl chloride in ethanol yields the corresponding *p*-nitrobenzyl sulfides in 97 and 68% yields, respectively (cf. also reaction (10)).



9

In both cases *Russell* obtained evidence for the radical anion **9** which establishes the involvement of the $S_{RN}1$ mechanism in the overall substitution. However, when R = Ph, the reaction is not retarded by addition of 10 mol% of *p*-dinitrobenzene or accelerated by illumination with visible light. When R = Me the effects also occur but are relatively small.

These results enable the mechanisms for substitution at Pt^{IV} to be viewed in a new light. It appears[93a] that only the base hydrolysis of $[Pt(NH_3)_5Cl]^{3+}$, *cis*-$[Pt(NH_3)_4Cl_2]^{2+}$, and *mer*-$[Pt(NH_3)_3Cl_3]^+$ are nucleophilic substitutions[94] at Pt^{IV} complexes. Most other examples should rather be considered as substitutions at the reaction center X^+ (X = halogen). — Nomenclature: reaction (20) is termed an



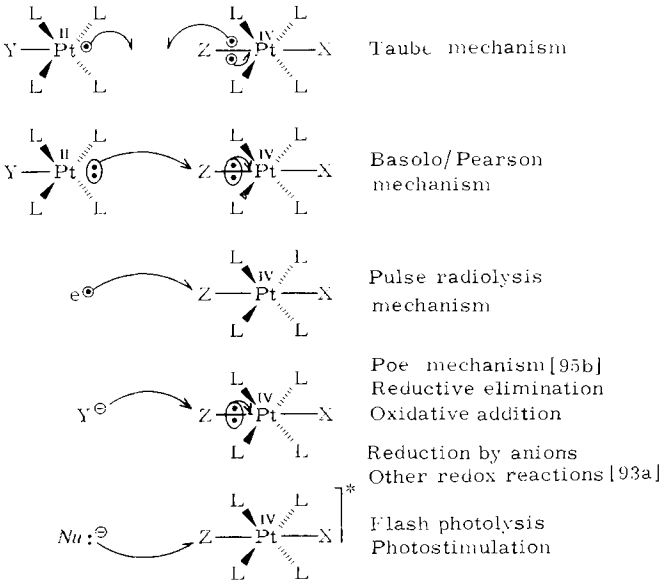
(20)

inner sphere atom transfer redox process or a two electron transfer process by inorganic chemists and a nucleophilic substitution on the electrophilic center X^+ by organic chemists.

The primary steps in substitutions at the center may be represented symbolically as shown in Scheme 6.

These simple schemes represent the perfect analogy[93b] that exists between the *Russell* experiment and the reactions of the platinum complexes. The main difference between *Russell*'s interpretation and the first step of the *Taube* catalysis is that *Taube*'s reducing agent $[Pt^{II}L_4Y]$ acts as an inner sphere reductant (reaction (17)). The consequence of this analogy is that, in our opinion, many reactions which have been described as involving a bridged mechanism are in *fact a combination of two mechanisms*. This obviously covers both substitutions[86] and reductions by anions[93a].

Since this hypothesis can be applied to several inorganic reactions we give some criteria which could be indicative



Scheme 6.

of such a combination. The first is the existence of photostimulation; this means that at least part of the mechanism involves a *Taube* initiation. The second is the demonstration that one electron reducing agents increase the rate of the reaction. The third is the unexpected hydrolysis products; H_2O can trap unstable Pt^{III} intermediates[55,56]. It is well known that the $S_{RN}1$ mechanism permits ready exchange of one or two ligands by water (see Section 3.13).

Application of these simple criteria could allow rapid reexamination of many results on substitution and reduction of Pt^{IV} compounds[62,78,86,93a]. Reaction (21), which

$$trans\text{-}[Pt^{IV}(en)_2Cl_2]^{2\oplus} + 2\,Br^{\ominus} \rightarrow trans\text{-}[Pt^{IV}(en)_2Br_2]^{2\oplus} + 2\,Cl^{\ominus} \quad (21)$$

undergoes photostimulation, has already been tested[48]. To obtain a reaction rate in the dark comparable to that obtained in light at 25 °C the solution temperature had to be raised to approx. 50 °C. For the reaction between $[Pt^{IV}(NH_3)_2(NO_2)_2Cl_2]$ and pyridine, photostimulation and Pt^{II} catalysis have been simultaneously observed[48].

5. ETC S in Square Planar Complexes

Does the parallel between organic and inorganic compounds, already established for "saturated" electrophilic centers, continue with unsaturated species?

5.1. Reductive ETC S

In 1954, *Taube et al.*[96] reported that the exchange between $[Au^{III}Cl_4]^-$ (d^8), and $^{36}Cl^-$ was greatly accelerated by addition of catalytic amounts of $[Fe^{II}(CN)_6]^{4-}$. A turnover of 10^4 $^{36}Cl^-$ per Fe^{2+} was observed. Other reducing agents (Sn^{II}, Sb^{III}, Au^I, V^{IV}) proved to be efficient catalysts but to a lesser extent than Fe^{II}. *Taube* proposed the mechanism shown in Scheme 7.

Initiation

$$[AuCl_4]^{\ominus} + [Fe(CN)_6]^{4\ominus} \xrightarrow[k_1]{SET} [AuCl_4]^{2\ominus} + [Fe(CN)_6]^{3\ominus}$$

Propagation

$$[AuCl_4]^{2\ominus} + {}^*Cl^{\ominus} \xrightarrow[\text{exchange}]{\text{rapid}} [AuCl_3{}^*Cl]^{2\ominus} + Cl^{\ominus} \qquad (22)$$

$$[AuCl_3{}^*Cl]^{2\ominus} + [AuCl_4]^{\ominus} \xrightarrow{SET} [AuCl_3{}^*Cl]^{\ominus} + [AuCl_4]^{2\ominus}$$

Termination

$$2\,Au^{II} \longrightarrow Au^{I} + Au^{III}$$

Scheme 7. *Cl = ^{36}Cl.

The kinetic law expected for such a mechanism with long chains was strictly followed. This mechanism differs from the $S_{RN}1$ mechanism: the direct exchange (step 22) would have to be replaced by a dissociative step followed by recombination with $^{36}Cl^-$ to parallel the $S_{RN}1$ mechanism. Tests recently proposed by *Bunnett* to distinguish between $S_{RN}1$ and $S_{RN}2$ should be applied to this reaction[97].

Transient Au^{II} species have been obtained by pulse radiolysis of $[Au^{III}Cl_4]^-$; it appears that the number of coordinating ligands is dependent on the concentration of free ligand in solution[98,99]. Very little is known about the dissociative ability of square planar d^9 complexes[100]. Quantitative data on the photostimulated chloride exchange have not been published, but the use of $[Au^{III}Cl_4]^-$ as a sensitizer in the photopolymerization of *N*-vinylcarbazole[101] suggests that $[Au^{III}Cl_4]^-$ could possibly be a better oxidant in the excited state.

5.2. Oxidative ETC S: Consequences for the Reactivity of Organic Substrates

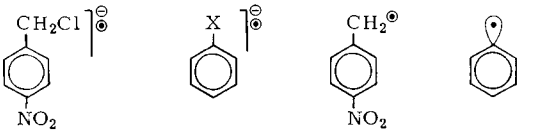
Until now we have only considered double activation reactions induced by reduction of the substrate: in the following we will show that ETC S can also occur by a mechanism that involves oxidation of the substrate as the first step.

A solution of $[Pt^{II}Cl_4]^{2-}$ (0.0125 mol/L) in presence of NaCl (0.0342 mol/L) and HNO_3 (0.062 mol/L) undergoes 1% exchange with radioactive chloride in 30 min at 0 °C. Addition of catalytic amounts of Ce^{IV} (5.5×10^{-4} mol/L), results in 87% exchange in 4 min. The proposed mechanism (Scheme 8) involves the generation of Pt^{III} intermediates[47].

Depending on the relative rates of SET and substitution, $[Pt^{II}Cl_3OH]^{2-}$ may or may not be observed as a secondary product in the exchange reaction.

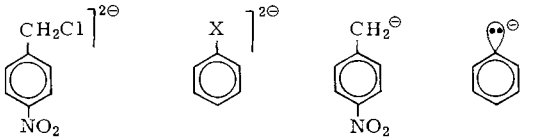
The really important conclusion is that an *oxidatively induced ETC mechanism* is possible. Furthermore, photostimulation operates in this system. The light catalyzed reaction of I^- and $[Pt^{II}Cl_4]^{2-}$ has been observed to be inhibited by thiosulfate ions, which probably indicates catalysis by Pt^{III}[102]. A closer look at anomalies in ligand exchange reactions[76,77] in Pt^{II} complexes could provide other examples of the oxidative ETC mechanism.

In organic systems active species can also either be generated by addition or by loss of an electron. In the $S_{RN}1$ mechanism the active species are either of type **10** or **11**, or of type **12** or **13**.



10 **11** **12** **13**

To obtain these species by oxidation the dianions **10a** and **11a**, or the sp^3 carbanion **12a** and the sp^2 carbanion **13a** must be used as starting agents.

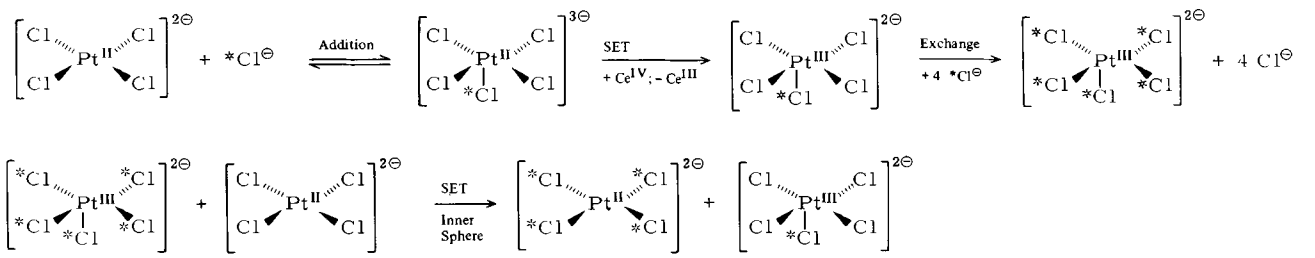


10a **11a** **12a** **13a**

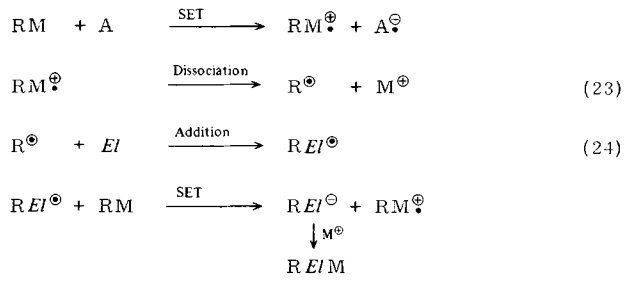
The generation of organic dianions in solution is usually difficult[103]. They can, however, be obtained fairly easily in aprotic solvents by electrochemical means[22a]. In presence of appropriate oxidizing agents (light may be the oxidizing agent, cf. Section 6.1.2) an oxidatively induced ETC reaction could be produced.

Carbanion intermediates pervade the whole of organic chemistry[104]. They usually do not exist (except in special cases[105]) as free species in solution but rather as ion pairs[106] or solvated ions[107]. Discussion will be limited to the example of the ETC mechanism in Scheme 9 which until now has not been applied to this field.

In this mechanism a catalytic oxidant (chemical or light) induces a chain reaction.

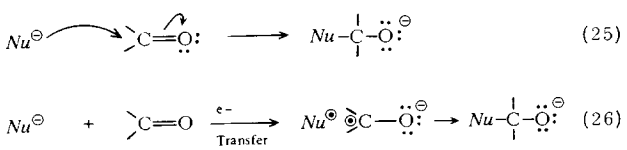


Scheme 8. *Cl = ^{36}Cl.



Scheme 9. *El* = electrophilic center; A = electron acceptor (possibly identical with *El*); M = metal or MgX; R = carbanion precursor.

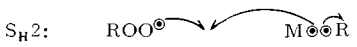
A clear distinction should be made between the ETC variant of DAISET, *i.e.* the double activation induced by single electron transfer and the "SAISET"[*] mechanism[109]. For example, it has been shown that small amounts of impurities in the magnesium seem to have a great effect on the kinetics of the reaction involving addition of Grignard reagents to aldehydes and ketones[110]. *House*[111] proposed the following scheme to rationalize the observed facts: One-step nucleophilic addition (reaction 25) and two-step electron transfer (reaction 26).



This reaction scheme (cf. [112]) corresponds to a competition between nucleophilic addition and a reductive SAISET mechanism: *i.e.* a special reactivity is induced in the carbonyl group by a single electron transfer. Most electrochemically induced reactions[109] are of this type. *House*'s results could also be interpreted as resulting from an oxidative DAISET S; set *El* = >C=O in reaction (24)[112]. Similarly, the formation of the Grignard reagent from magnesium and an alkyl halide, which is known to be catalyzed by oxidizing agents[113, 114] and sensitive to irradiation[114a], could be regarded as an oxidative DAISET reaction. In this case, it could give some interesting clues for the heterogeneous catalysis in solution[115].

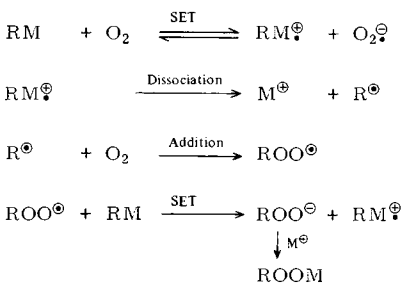
The oxidative ETC mechanism has also never been considered for the autoxidation of boranes, which has been viewed as a chain mechanism[108b, 116] similar to that involved in the autoxidation of other organoelement compounds[117].

Furthermore "Bimolecular Homolytic Substitution at a Metal Center" (S_H2) mechanism, depends on this reaction type:



The chain mechanism for the autoxidation is probably correct; in the ETC alternative (Scheme 10), which has not previously been considered, the S_H2 step can be circumvented.

The discussions on this point are misleading since they suggest that the S_H2 and electron transfer mechanisms



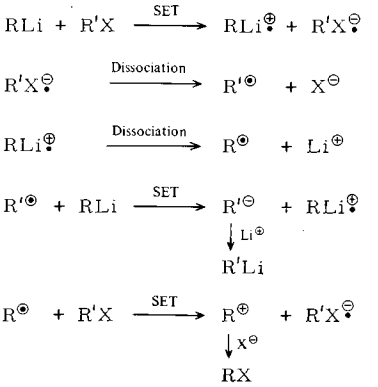
Scheme 10.

only differ in the degree of charge separation in the transition state[118]. In the ETC process, $ROO^{\ominus}$ attacks another metal center.

The possibility of a ETC mechanism has also been neglected in the interpretation of CIDNP results. In a review on CIDNP[119] theory it is stated that no CIDNP effect was found in the reaction of *tert*-butyllithium with *n*-butyl iodide at −70 °C under conditions where rapid halogen-metal exchange, but no C—C coupling occurs[120]. This indicates that no electron transfer occurs in the exchange

RLi + R'Hal → RHal + R'Li

in spite of earlier reports[121]. The ETC alternative where electron transfer is followed by a chain reaction, so that there is the possibility that the initial polarization can relax, is not discussed (Scheme 11).



Scheme 11. Other possibility: S_H2 reaction of R with R'X (see [47b, 304]).

6. More about the ETC Concept

6.1. The First Activation

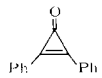
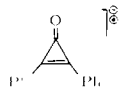
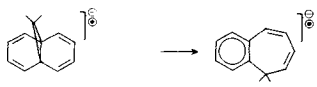
6.1.1. Quantitative Estimation

We have defined the first activation in the ETC mechanism as *the transfer of a single electron* to/or from the substrate to be activated.

Reductive activation can spectacularly enhance molecular reactivity. Some results are gathered together in Table 4. There are also a number of systems that do not change their reaction behavior upon oxidation or reduction. For example, V^{III} and V^{II} exhibit almost identical rates of exchange of water between the coordination sphere and sol-

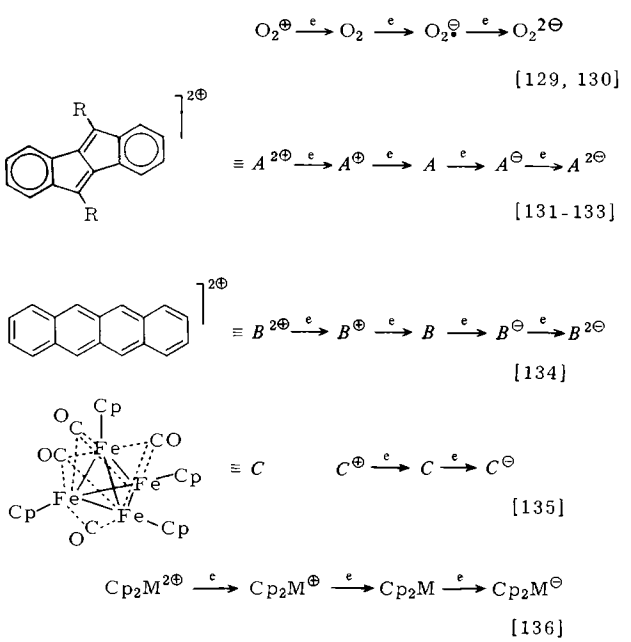
[*] SAISET = "*S*ingle *A*ctivation *I*nduced by *S*ingle *E*lectron *T*ransfer".

Table 4. The first activation in the ETC mechanism.

Reaction type	k (M^0)	k ($M^{\ominus}$) [a]	Ratio [b]	Ref.
$[Cr^{III}(H_2O)_6]^{3\oplus} + H_2O^* \rightarrow [Cr^{III}(H_2O)_5H_2O^*]^{3\oplus} + H_2O$	3×10^{-6}			[122]
$[Cr^{II}(H_2O)_6]^{2\oplus} + H_2O^* \rightarrow [Cr^{II}(H_2O)_5H_2O^*]^{2\oplus} + H_2O$		10^{9}	10^{-15}	[122]
$[Ru^{III}(H_2O)_6]^{3\oplus} + H_2O^* \rightarrow [Ru^{III}(H_2O)_5H_2O^*]^{3\oplus} + H_2O$	$< 10^{-6}$			[122]
$[Ru^{II}(H_2O)_6]^{3\oplus} + H_2O^* \rightarrow [Ru^{II}(H_2O)_5H_2O^*]^{2\oplus} + H_2O$		10	10^{-7}	[122]
$PhCO_2^{\bullet\oplus} \rightarrow CO_2 + Ph^{\bullet\oplus}$	$\approx 10^{5}$			[124]
$PhCO_2^{\ominus} \rightarrow CO_2 + Ph^{\ominus}$		10^{-6}	10^{11}	[125]
 $\rightarrow$ PhC≡CPh + CO	[c]			[126]
 $\rightarrow$ PhC≡CPh + CO		[d]		[127]
	$\approx 10^{-12}$			[127]
		10^{3}	10^{-15}	[127]

[a] Reduced form. [b] $k(M^{II})/k(M^{\circ}) < 1$: reductive activation; $k(M^{II})/k(M^{\circ}) > 1$: oxidative activation. For further examples of reductive activation, see [128]. [c] Thermal CO cleavage at 150 °C. [d] Lifetime of the initial radical at −90 °C; 20 min.

vent[122]. The study of electrochemical reduction of halogenosilanes and halogenogermanes demonstrated that their radical anions tend to dissociate less than their haloalkane counterparts[123]. Some molecular species are dissociatively inert over a range of oxidation states (Scheme 12).



Scheme 12. Cp = cyclopentadienyl, M = Ni or V.

It is of note that until now, little theoretical work has been carried out to investigate the dependence of the reactivity on the oxidation state. A simple approach would be to examine the LUMO since if this is strongly antibonding, the molecular species would be strongly dissociatively activated by reductive initiation; in contrast, if the HOMO is strongly bonding the species could be easily oxidatively activated[137-139]. These statements are probably not sufficient. SCF-X_α molecular orbital calculations could be a starting point for more detailed investigations (cf. [140]).

6.1.2. The Photon as a Chemical Reagent

Kochi recently stressed the equivalence of the terms "charge transfer" (organic vocabulary) and electron transfer (inorganic vocabulary)[108c]. An examination of the literature of organic chemistry shows that while the acid/base properties of excited states[141] have frequently been investigated, their redox properties have, with some exceptions[142], been neglected. *Balzani et al.* in their review articles[143] clearly emphasized several very important points for inorganic systems: species that are in excited states may be quenched in bimolecular processes involving electron transfer reactions, and that an excited state may be *both* a better oxidant and a better reductant than the ground state. For example the excited complex $[Ru^{II}(bpy)_3]^{2+}$ (bpy = 2,2′-bipyridyl) can both reduce and oxidize water[144]. This explains in part the enormous increase in interest in the photochemistry of such complexes and their possible role as catalysts in the conversion of light into chemical energy[145].

To transfer or accept an electron, an excited state must have a lifetime longer than 10^{-9}–10^{-10} s[143c]. This is quite normal for organic molecules, but transition metal complexes usually have shorter lifetimes. However, here again the ETC concept can add a new dimension. If the primary electron transfer is of very low efficiency (low primary quantum yield) due to the short lifetime of the excited state, but induces a fairly long chain, then neglected chemical reactions assume significance. For example, much of

the photochemical reactivity of $[Pt^{IV}X_6]^{2-}$ complexes has been rationalized (see [146d], p. 227) on the basis that the primary step in the photoexchange reaction is reaction (14).

$$[Pt^{IV}Cl_6]^{2\ominus} \xrightarrow{h\nu} [Pt^{III}Cl_5]^{2\ominus} + Cl^{\odot} \qquad (14)$$

The hypothesis

$$[Pt^{IV}Cl_6]^{2\ominus} + Cl^{\odot} \rightarrow [Pt^{III}Cl_6]^{3\ominus} + Cl^{\oplus} \qquad (1')$$

good oxidant in the excited state

$$[Pt^{III}Cl_6]^{3\ominus} \rightarrow [Pt^{III}Cl_5]^{2\ominus} + Cl^{\odot} \qquad (2')$$

has never been formulated[146], probably because it is assumed that the lifetime of the excited state is too short. When it is considered that in flash photolysis experiments addition of X^- accelerates the appearance of the transient[68], reexamination of this rationalization in Pt^{IV} photochemistry could be worthwhile. This also applies to many other photochemical reactions where a step currently interpreted as an induced homolysis could just as well be rationalized by SET in the excited state, inducing bond dissociation followed by a chain reaction[147, 148].

An interesting property of the photon is that, due to the short lifetime of excited states, it probably mainly induces one electron exchanges between the redox couple. This may be useful in mechanistic studies. Another favorable property of the photon is that it disappears after the induction reaction, in contrast to "normal" chemical reagents that may shorten the chain. On the other hand it could be expected that the synergic criteria (Section 3.14) involving the double experiment "scavenging of radicals + photostimulation" can sometimes break down. It is possible to imagine some species whose excited-state lifetime is not long enough to allow an electron transfer, or whose range of photoexcitation is beyond the usually accessible wavelengths.

Interesting applications resulting from combinations of photochemistry and electrochemistry have been recently reported and these extend the scope of the photon as a reagent to an even greater extent[149].

6.2. The Second Activation

It is very difficult *a priori* to answer the question of whether a reaction chain is formed or not. *Savéant et al.*[21b] proposed the relation $E_2^0 < E_1^0$: E_2^0 and E_1^0 are the standard potentials for the reactions

$$ArylNu^{\ominus} - e \rightleftharpoons ArylNu \quad \text{and}$$
$$ArylX + e \rightleftharpoons ArylX^{\ominus}$$

(see Scheme 1). This does not, however fully resolve the problem because:

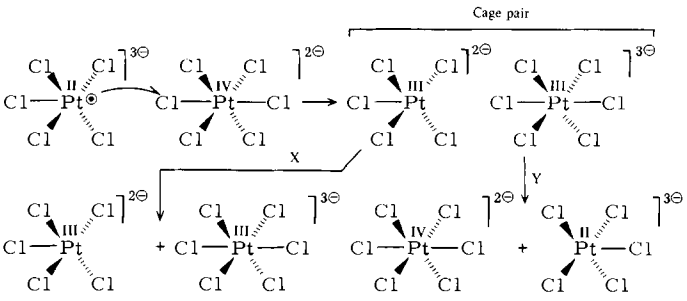
Savéant et al. later demonstrated that for halobenzene and halopyridine substrates this criterion need not be fullfilled for the $S_{RN}1$ mechanism to be observed[21d].

For isotopic exchange reactions (Section 4.1) $E_2^0 = E_1^0$.

Most of the tabulated data[150] concern the half-wave potentials ($E_{1/2}$) rather than actual standard potentials. The use of these $E_{1/2}$ values instead of standard potentials is problematic: the $E_{1/2}$ values of *p*-substituted benzyl chlorides are apparently not correlated with the ease of benzyl radical production. The discrepancies can be quite large; for example, *Flesia*[151] recently evaluated, from $E_{1/2(red)}$ of *p*-nitrobenzyl chloride and $E_{1/2(ox)}$ of thiophenoxide that only 10^{-18} mol/L of the *p*-nitrobenzyl chloride radical anion is present in solution. This value is probably too low. There is clearly a lack of semiempirical methods[152] for estimating standard potentials from half-wave potential values, and more generally an uncertainty about factors which stabilize radical species[153, 154]. All this shows that at present the best way to answer the proposed question is experimentally.

6.3. SET Mechanism or S_N2 Reaction? The "Retro-CIDNP" Alternative

Flesia[151] has proposed a provocative model for the unification of SET- and S_N2-pathways. In this model, $S_{RN}1$- and S_N2-reactions proceed by almost identical routes. In both cases the nucleophile first gives up an electron to the electrophilic center and the selection between $S_{RN}1$ and S_N2 paths occurs within the radical pair. If the two radicals recombine in the cage (Y), the normal S_N2 process occurs, whereas if they can escape from the radical pair and initiate a chain, the $S_{NR}1$ mechanism takes place. For the exchange at $[Pt^{IV}Cl_6]^{2-}$, catalyzed by $[Pt^{II}Cl_4]^{2-}$ this process can be formulated as in Scheme 13.



Scheme 13. The steps (2'), (3')... follow (X, Y, see text).

Flesia's model has been subjected to strong criticism from organic chemists[155d], but it can be taken as a working hypothesis. The different mixtures of products in a chemical reaction are normally related to a Boltzmann distribution of the transition states: twice as much of product A as product B is obtained if the difference $\Delta\Delta G^{+}$ between the processes leading to A and B is *ca.* 400 cal/mol. The results of *Surzur et al.*[28] and *Russell et al.*[45] must answer the question: what factors determine the competition between a chain and a non-chain process and at what precise step is the Boltzmann distribution to be considered?

We propose that the Boltzmann distribution becomes important in the common cage pair—in accord with *Flesia*'s hypothesis—but we extend the reasoning further. One can imagine that the ETC process allows the revelation of phenomena always present in exchange reactions, but seldom seen because they are unfavored in the Boltzmann distribution by a $\Delta\Delta G^{+} \geq 3$ kcal. This follows from the fact

that the "impurity" created can enter a chain with a rate far greater than that of the normal exchange reaction. This "impurity" may be formed either when the solvent cage is loose enough to allow the primary radical pair to escape (SET may occur at distances greater than 10 Å) or when a singlet-triplet transition promotes formation of this species. The phenomenon, always present in exchange reactions, is a type of "retro-CIDNP effect". *Kaptein et al.*[157a,b] and *Closs et al.*[157c,d] proposed that in any homolytic cleavage of a bond there is a favorable separation where the crossing of singlet and triplet states can occur. These two states, always present in pairs of radicals usually do not mix and even the mixing occurring at the most favorable separation is very weak. The CIDNP phenomenon enhances this effect through magnetic resonance[158]. The phenomenon can, in our opinion, also be enhanced by building a chain long enough to balance the $\Delta\Delta G^{+}$ difference: we term this the "retro-CIDNP effect" because now the *S-T* crossing takes place in the formation of the bond. Because of the chain nature of the process, it is difficult to detect it by NMR measurements. However, the action of appropriate magnetic fields[159] on chemical reactivity[7,8a] should make it possible to confirm or reject this hypothesis. *Sagdeev*[30] has recently published an authoritative review which should allow the best experimental conditions to be chosen (temperature, viscosity of the solvent) for the demonstration of magnetic effects on $S_{RN}1$ reactions. An alternative could be to show that one of the two main reactions studied by *Sagdeev*

$$RCl + n\text{BuLi} \xrightarrow[t=40\,^{\circ}C]{\text{hexane}} RBu + RR + LiCl + C_8H_{18} \quad [160a]$$

$$ArylN_2^{\oplus} + RO^{\ominus} + ROH \longrightarrow ArylH + N_2 + \ldots \quad [160b]$$

actually involves an ETC mechanistic pathway.

Despite the fact that carbanions[161], trimethylsilyl-[162], trialkylstannyl-[163a,b] and trialkylgermyl-anions[163c] are excellent electron transfer reagents it is only for the two last anions that an $S_{RN}1$ mechanism has been proposed. *Quintard* and *Pereyre et al.*[46,163] demonstrated that for

$$PhX + Bu_3SnLi \rightarrow PhSnBu_3 + LiX$$

an $S_{RN}1$ mechanism (short chain type) and a classic halogen metal exchange mechanism (and possibly others) compete. This kind of competition was also found in the reaction between bromo- or iodobenzene and R_3GeLi[163c].

An experiment which could transfer the problem of SET *versus* S_N2 from the field of semantics to an experimentally answerable question[156] would be significant. Investigations of the role of spin-orbit coupling[164] in bimolecular reactions could provide information on molecular motions in and out of the solvent cage[165], and their behavior in collisions[166].

6.4. Experimental Difficulties in the Study of ETC Processes

How can we measure the proportion of each process in the overall reaction? Two problems of very different difficulty must be distinguished there. The first is dealt with qualitatively and answers whether the reaction proceeds *via* two simultaneous processes (cf. [108f,167]). The second is the quantitative estimation of each mechanism under various conditions; consideration of the fundamentals of the ETC concept (Section 6.1) immediately indicates how laborious this task is.

Two examples of the obstacles encountered in using the concepts of scavengers and catalysts are given: Studies of the exchange reactions at Pt^{IV} involving inhibition of light induced substitution reactions of $[Pt^{IV}Br_6]^{2-}$ and $[Pt^{IV}I_6]^{2-}$ by $[Ir^{IV}Cl_6]^{2-}$ indicated that the spectrum of $[Ir^{IV}Cl_6]^{2-}$ rapidly disappeared in the presence of iodide, although the inhibitory properties appeared to be retained[168]. $[Ir^{IV}Cl_6]^{2-}$ is extensively used to suppress the participation of the ETC mechanism in reductive elimination/oxidative addition reactions[95,196] and it may be asked if the ETC reaction is completely suppressed[108f]. The exchanging nucleophile *often functions as a reducing agent.* In the original work by *Taube et al.*[47] the concentration of nucleophile was far less than that of the complex (*e.g.*: $[Pt^{IV}Cl_6]^{2-}$ 0.039 mol/L; Cl^{-} 0.0087 mol/L), in which case the effect of quenchers was meaningful. In most of the later studies, however, the concentration of nucleophile was considerably higher: in a typical run *Poë et al.* studied a solution 9×10^{-5} mol/L in $[Pt^{IV}Br_6]^{2-}$, 5×10^{-2} mol/L in I^{-} and 8×10^{-6} mol/L in $[Pt^{IV}Cl_6]^{2-}$[95b]. A further example is provided by the report by *Elding et al.*[91], who found that the rate of the reaction in the dark was unaffected by addition of small concentrations of Fe^{III}. When it is realized that a large excess of the reducing species Pt^{II} is also present in these experiments in the dark it can be asked whether the mechanism for the dark reaction does not probably involve Pt^{III} catalysis[91]. The problem is increased by the fact that scavengers may be an unrecognized part of the reaction mixture: *Dreyer*[51] has shown the presence of Br_2 in commercial HBr and *Grinberg et al.*[170] has shown that under certain pH conditions $[Pt^{IV}X_6]^{2-}$ releases X_2 into solution.

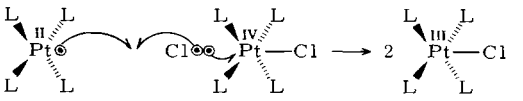
The precise determination of quantum yields for photostimulated ETC reactions is also very troublesome. *Stranks* and *Yandell*[80] have proved that the light intensity exponent can easily rise from 0.5 to 0.7 in solutions containing micromolar concentration of impurities.

6.5. Scope of the ETC Concept

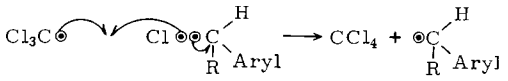
6.5.1. More about Chain Reactions

According to *Cotton* and *Wilkinson*'s[171] generalized definition, complexes are species, charged or uncharged, in which a central atom is surrounded by a set of atoms or ligands (CH_4 is a complex within this definition). This definition is convenient to use in investigating the scope of ETC S.

However, as we intend to cover most molecular species within this approach, we must first clarify a particular point of nomenclature. In the inorganic nomenclature an inner sphere redox process may be represented as



and in organic nomenclature the S_H2 process is written[108d, 172]



A major difficulty in the extension of the inner sphere definition to S_H2 reaction arises from ambiguities in the determination of the oxidation number of carbon[173]. For this reason S_H2-induced chain reactions will not be discussed.

A representation of complexes describing both inorganic and organic species must specify:
The coordination number m, the total charge q, and the number of unpaired electrons s.

The same representation covers both electron acceptor and electron donor complexes:

$$[ML_m]^q_s \quad \text{and} \quad [M'L'_{m'}]^{q'}_{s'}$$

For example in CH_3S^-: M' = C, L' = H, S, q = −1, s = 0.

Within these conventions, a typical $S_{RN}1$ mechanism is shown in Scheme 14:

Initiation

$$[ML_m]^q + [M'L'_{m'}]^{q'} \underset{\text{outer sphere}}{\overset{\text{SET}}{\rightleftharpoons}} [ML_m]^{q+(-1)} + [M'L'_{m'}]^{q'-(-1)}$$

acceptor donor

Propagation

$$[ML_m]^{q+(-1)} \xrightarrow{\text{dissociation}} [ML_{m-1}]^{q+(-1)} + L$$

$$[ML_{m-1}]^{q+(-1)} + [M'L'_{m'}]^{q'} \xrightarrow{\text{association}} \underbrace{[ML_{m-1}]^{q+(-1)}[M'L'_{m'}]^{q'}}_{\text{pair}}$$

$$\text{pair} + [ML_m]^q \xrightarrow{\text{SET}} [[ML_{m-1}]^q[M'L'_{m'}]^{q'}] + [ML_m]^{q+(-1)}$$

Scheme 14.

The value of s must be examined for every particular case because of the filling of d orbitals in transition metal complexes. The extention to charged ligands is easy. The general Scheme 14 may be modified to represent an ETC reaction where the initiation step is an inner sphere single electron transfer.

$$[ML_m]^q + [M'L'_{m'}]^{q'} \xrightarrow[\text{inner sphere}]{\text{SET}} [ML_{m-1}]^{q+(-1)} + [M'L'_{m'}L]^{q'-(-1)}$$

$$[ML_{m-1}]^{q+(-1)} + [M'L'_{m'}]^{q'} \rightarrow \underbrace{[ML_{m-1}]^{q+(-1)}[M'L'_{m'}]^{q'}}_{\text{pair}}$$

$$\text{pair} + [ML_m]^q \xrightarrow{\text{SET}} [ML_m]^{q+(-1)} + \underline{[ML_{m-1}]^q[M'L'_{m'}]^q}$$

$$[ML_m]^{q+(-1)} \rightarrow [ML_{m-1}]^{q+(-1)} + L$$

etc....

Scheme 15.

Scheme 15 corresponds to the case where a strong primary activation is needed: the reducing agent initiates the chain, which then propagates without further assistance. The general oxidative ETC S mechanism could be written according to the same principles (Section 5.2).

These general mechanisms can be modified according to need; an exhaustive study of the ETC concept could reveal new chain reactions or combinations of chains[174]. Enzymatic catalytic chains[175] indicate that even apparently simple reactions must be explained by fairly elaborate combinations of ETC mechanisms.

6.5.2. The SET Matrix

In a publication dealing with the unification of the S_N2 and SET mechanisms (cf. Section 6.3), *Flesia*[151] proposed an ingenious matrix to represent the possibilities of single electron transfer between organic species. Figure 1 illustrates how the matrix can be extended from organic chemistry to all molecular species. In principle, any of the single electron transfers described in this matrix could be the starting point for a chain reaction with the possibility of an ETC process.

For organic molecular reactions, however, only the two cases

$$Nu^{\ominus} + RX \quad \text{and} \quad Nu + RX$$

have been proven to react according to an ETC mechanism.

6.5.3. The Relationship between Electronic Configuration and Reactivity in Transition Metal Complexes

If one wishes to predict which types of transition metal complexes might be expected to undergo exchange reactions of the ETC-type it is necessary to take a number of factors into consideration. In the first place the substrate should be substitutionally inert, *i.e.*, the simple substitution reaction should be slow enough to allow the alternative mechanism to make a major contribution to the overall process. The intermediate of lower or higher oxidation state must be substitutionally more labile than the substrate, and the redox reaction between the intermediate and the substrate should also be fast[82], thereby allowing a chain reaction to occur. Finally, the relative stabilities of the oxidation states[208] should be considered since these will be of importance to initiation and termination processes. The electronic configuration and formal charge of the reaction center serve as a basis for classification. Redox potentials and the rates of redox processes are also very sensitive to the nature of the ligands attached to the reaction center[82].

The simplest and shortest way of discovering transition metals where ETC S can occur is to use the "angular overlap" model[210]. It is, however necessary to reiterate that the lability of a particular leaving group will be very dependent upon its properties: the published rate constants for the exchange of X by H_2O in the complex $[Co(NH_3)_5X]^{n+}$ cover a range of at least 5 orders of magnitude[209]. The following treatment is therefore only an approximate guideline.

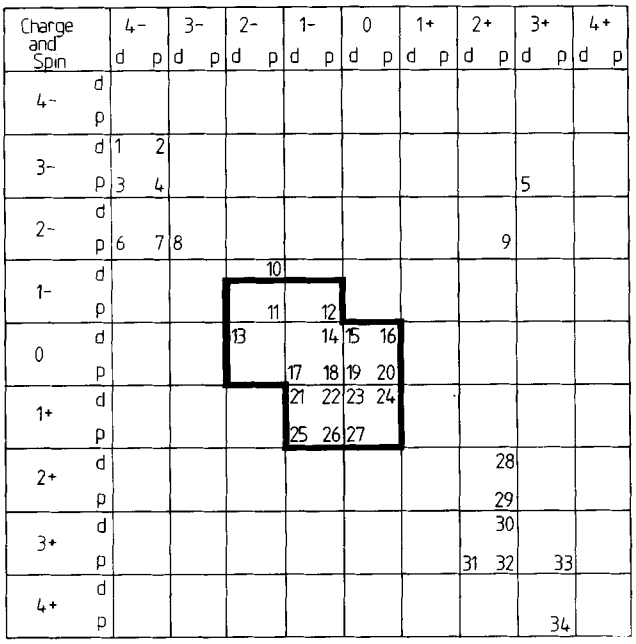


Fig. 1. Matrix showing some possible reactions between molecules and complexes. No attempt has been made to be comprehensive. d signifies a diamagnetic, p a paramagnetic species. For inorganic species this data comes from [176]. The numbers given in the squares refer to the examples below (number, donor + acceptor, reference). Examples from organic chemistry are located in the enclosed area.

1: $[W(CN)_8]^{4-}$ + $[Mo(CN)_8]^{3-}$ [177]
2: $[Fe(CN)_6]^{4-}$ + $[Mo(CN)_8]^{3-}$ [177]
3: $[W(CN)_8]^{4-}$ + $[Fe(CN)_6]^{3-}$ [177]
4: $[Fe(CN)_6]^{4-}$ + $[Fe(CN)_6]^{3-}$ [178]
5: $[Co(NH_3)_5(4,4'\text{-bpy})]^{3+}$ + $[Fe(CN)_5(H_2O)]^{3-}$ [179]
6: $[W(CN)_8]^{4-}$ + $[IrCl_6]^{2-}$ [177]
7: $[Fe(CN)_6]^{4-}$ + $[IrCl_6]^{2-}$ [180]
8: $[IrCl_6]^{3-}$ + $[IrCl_6]^{2-}$ [181]
9: $[Cr(H_2O)_6]^{2+}$ + $[IrCl_6]^{2-}$ [182]
10: $[MnO_4]^{2-}$ + $[MnO_4]^{1-}$ [183]
11: aromatic dianion + associated radical anion [184]
12: perylene radical anion + perylene radical anion [185]
13: perylene dianion + *p*-dichlorobenzene [186]
14: radical anion + neutral paramagnetic molecule [187, 188]
15: R_3N + trinitrobenzene [189]
16: 1-ethyl-4-methoxycarbonylpyridyl radical + 4-nitrobenzyl chloride [190]
17: phenoxide ions + phenoxyl radicals [191a]
coupling of radicals with nucleophiles [191b]
18: naphthalene radical anion + alkyl radicals [192]
19: principle reported in [193]; no precise examples given
20: $(CH_3)_3CH_2^-$ + *m*-$ClC_6H_4CO_2^-$ [194]
21: carbanion + $[Aryl_2I]^+$ [195]
22: naphthalene radical anion + 4-substituted 1-methylpyridinium halides [196]
23: *N*-methylcarbazole + tropylium tetrafluoroborate [197]
24: $Ph_2C(OH)^-$ + 4-cyano-1-methylpyridinium iodide [196]
25: halide ions + perylene radical cation [198]
26: aromatic radical anion + benzoyl peroxide [199]
27: ArylH + $(Aryl'H)^+$ [200]
28: $[Cr(H_2O)_6]^{2+}$ + $[Co(NH_3)_6]^{3+}$ [201]
29: $[Cr(H_2O)_6]^{2+}$ + $[Cr(H_2O)_5OH]^{2+}$ [202]
30: $[Co(H_2O)_6]^{2+}$ + $[Co(H_2O)_6]^{3+}$ [203]
31: $[Ru(NH_3)_6]^{2+}$ + $[Ru(ND_3)_6]^{3+}$ [204]
32: $[Fe(H_2O)_6]^{2+}$ + $[Fe(H_2O)_6]^{3+}$ [205]
33: $[V(H_2O)_6]^{3+}$ + $[Fe(H_2O)_6]^{3+}$ [206]
34: $[Pu(H_2O)_n]^{3+}$ + $[Pu(H_2O)_n]^{4+}$ [207]

The angular overlap model[210] tentatively estimates the energies of the d orbitals in both the ground (O_h) and transition state (D_{3h} or D_{4h}) of a dissociative substitution. If the difference between these two energies is less than a given value, the complex is predicted to be "labile". *Purcell et al.*[210a] applied this principle to the dissociation substitution of O_h complexes and found the results given in Table 5. For our purposes the use of Table 5 is quite simple: if when adding an electron to the configuration one passes from an inert complex to a labile one, then a reductive ETC S process is possible. The reverse reasoning applies to oxidative ETC S processes.

Table 5. Electron Configurations and lability of octahedral transition metal complexes (see [85a], p. 720). l.s. = "low spin", h.s. = "high spin".

Configuration		Transition state or intermediate	
		C_{4v} Tetragonal pyramidal	D_{3h} Trigonal pyramidal
d^0, d^1, d^2, d^3		inert	inert
d^4, d^5, d^6	l.s.	inert	inert
	h.s.	labile	labile
d^7	l.s.	labile	inert
	h.s.	labile	labile
d^8		labile	inert
d^9, d^{10}		labile	labile

d^3-Systems V^{II}, *Nb^{II}*, *Ta^{II}*, Cr^{III}, *Mo^{III}*, *W^{III}*, Mn^{IV}, *Re^{IV}* are possible candidates for reductive ETC S reactions. Ligands favoring high spin states in the d^4-configuration should be preferred (Table 5). The quintet state of the first row d^4-elements leads to extremely labile complexes especially for Cr^{II}. There are many cases of exchange reactions at Cr^{III} that are catalyzed by Cr^{II}[211], among which is the method of dissolving the insoluble anhydrous $CrCl_3$ in water by addition of a small amount of a reducing agent ($SnCl_2$, Zn or Cr^{II})[171b]. Since Δ_0 increases with the heavier homologues within a given group, d^3-octahedral complexes (printed in italics for the above elements) should not be suitable for ETC S reactions. Moreover, V^{II} and V^{III} ions exchange water at similar rates[122].

The d^6-low spin configuration in Mn^{I}, Re^{I}, Fe^{II}, Ru^{II}, Os^{II}, Co^{III}, Rh^{III}, Ir^{III}, Ni^{IV}, Pd^{IV}, and Pt^{IV} is also suitable for reductive ETC S processes (Table 5). Because of their low spin states, organometallic compounds of first row elements and complexes of heavier elements surrounded by "weaker" field ligands should be preferred as possible candidates. It is encouraging to find that according to the very crude angular overlap model, Pt^{IV} and Rh^{III} are among the possible ETC S candidates. Reductive ETC behavior, although differently interpreted, has effectively been found in Co^{III}[212–215], Ir^{III}[216], Rh^{III}[86, 217–220], and Pt^{IV} (cf. Section 4).

An octahedral complex with more than six d-electrons would exceed the 18-electron rule which, though possible, is not usual[221].

For oxidative ETC reactions, Table 5 predicts only d^8-octahedral complexes as possible candidates (*e.g.* Ni^{II}).

When square planar complexes are considered, the angular overlap model is less useful, because the dissociative mechanism rarely operates. The only guideline is to assume reductive ETC S reactions are possible for the d^8-configuration (Rh^{I}, Ir^{I}, Ni^{II}, Pd^{II}, Pt^{II}, Au^{III}); such a mechanism has been discovered for Au^{III} (Section 5.1). The process described for Pt^{II} complexes in Section 5.2 also serves as a reference point.

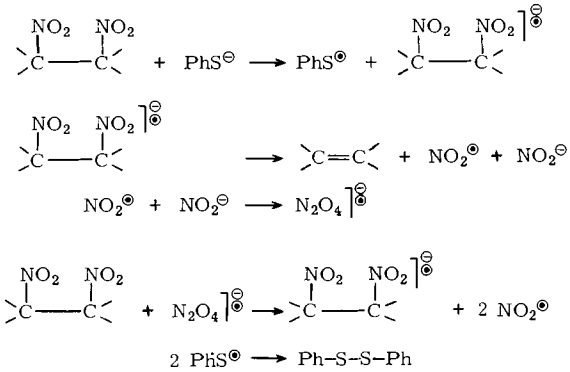
Data for complexes with higher coordination numbers would be interesting; it is known that $[Mo^{V}(CN)_8]^{3-}$ reacts photochemically with quantum yields > 1[222].

In the foregoing discussion we purposely omitted discussion of organotransition-metal reactions. Some recent examples suggest that the ETC mechanism also operates in this field[45, 223, 224]. The often polarizable organometallic compounds[225] could behave as good electron donors[226] in the first ETC step (*e.g.* in oxidative additions[227]).

6.5.4. ETC E, A, Ra, Re, Ox

There have been several attempts to underline the importance of chain homolytic processes, and of redox catalysis[224]. However, even if these approaches were important steps towards understanding the reaction mechanisms, they were perhaps still insufficient to bring about satisfactory overall coherence. For example in none of the best recent reviews on the topic of redox activation[224, 228] is *Kornblum*'s work on the $S_{RN}1$ mechanism cited. The examples already discussed in the present article illustrate how informative the application of the ETC concept may be in apparently unrelated fields. Until now we have focussed on the ETC S mechanism, but to show the generality of the approach, examples of ETC E should be presented (elimination), A (addition), Ra (Ra rearrangement) (classification, see [1a]).

Scheme 16 shows a typical example of ETC E[17, 229]:

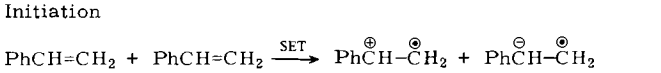


Scheme 16.

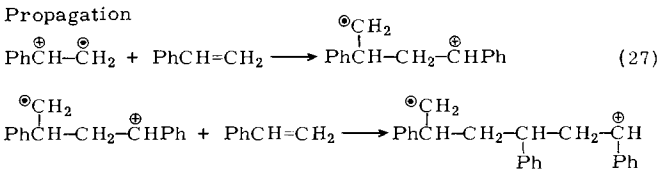
Highly hindered alkenes may be obtained using this process. It corresponds to a reductive ETC process of the educt. Examples of oxidative ETC E are found in organometallic compounds.

The polymerization of styrene[230] could tentatively be given as an example of ETC A (Scheme 17).

Initiation



Propagation

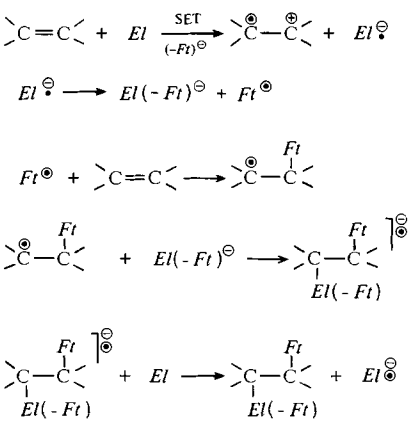


(27)

Scheme 17. The process is promoted by traces of oxidizing or reducing agents.

Here we present only the radical cation chain; the rapid formation[139, 231] of tetracyclic systems from *anti*-[2.2]metacyclophane when treated with an alkali metal, and the behavior of "living polymers"[232] show that a radical-anion chain can equally develop. The ETC A mechanism explains why small amounts of O_2 favor "spontaneous" styrene polymerization and are in accord with a photochemical initiation reaction[233] which provides polymers whose molecular weight distribution is the same as that obtained by thermal polymerization. It is very difficult to know if the "spontaneous" polymerization proceeds analogously to reaction (27); the reaction order[234] for the "spontaneous" chain reaction is not entirely in accord with this.

The ETC A scheme is not limited to polymerizations. The activation of unsaturated reaction centers (C=C, C≡C, C=N, C=M, M=N, ...) could be conceived as shown in Scheme 18.



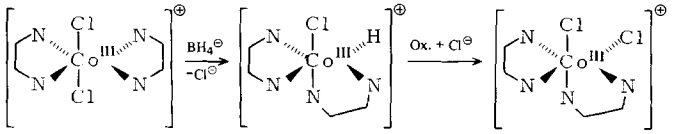
Scheme 18. *El:* electrophilic species; *Ft:* molecular fragment.

At this point it must be mentioned that the usual description of reaction mechanisms clearly stresses the stoichiometric result. If one adopts another nomenclature based on "the direction of travel of electron densities", then *e.g.* olefins become generalized nucleophiles and can donate one electron to a chosen electrophilic substrate. Following this idea, the one-track minded ETC chemist is led unavoidably to the conclusion that competition between ionic and radical addition of HBr to olefins[235] is an example of the ETC concept. It is easy to write down a ETC scheme in which the chain carrier species is $HBr^{\bullet}$ formed by a SET process between the olefin (donor) and HBr (acceptor). However, here we meet a difficulty already stressed by *Hoz* and *Bunnett*[14] (cf. Section 6.1.2): plausible initiation mechanisms can be formulated to account for initiation either by iodobenzene-absorbed photons or by CT-absorbed photons. When does the photon act as a direct homolytic breaker of bonds and when does it create a highly reducing or oxidizing species able to induce the same fracture of the bond?[236] A clear answer to this question would avoid excessive extension of the ETC concept to reaction mechanisms. A straightforward look at the difference in electron affinity of the acceptor and ionization potential of the donor should indicate if the initial single electron transfer SET is feasible[237]. A threshold problem nevertheless remains: consideration of half-

wave redox potentials leads to the conclusion[151] that the first step may be such that not more than 10^{-18} mol/L of the initiator species is present in the reaction between *p*-nitrobenzyl chloride and thiophenoxide (cf. however Section 6.2). The threshold problem is important because there is no reason not to consider the very weak bases C—H and C—C as electron donors[238] to the appropriate oxidizing agents. A final point raised by the "electron density flux" concept is that of oxidative or reductive ETC mechanism. Within this concept, the example of oxidative ETC reactions that (Section 5.2) becomes a special kind of reductive ETC reaction: RMgX is a generalized reducing species which donates an electron. The new fact then is that in this case the "nucleophile" is activated by a SET and the question arises: which mechanism prevails when both the nucleophile and the electrophile could be dissociatively activated (RMgX + RX)? Appropriate addition of reducing or oxidizing agents could perhaps selectively favor one of the two possible chains when both develop. Puzzling organometallic reactions[239] could possibly be explained by *Emmanuel*'s masterful review on selectivity of chemical reactions dealing with competition between chain reactions[240].

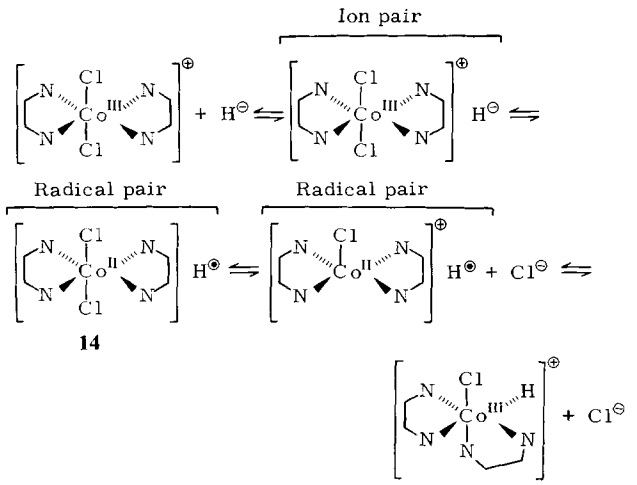
The rearrangement of *trans*-$[Co^{III}(en)_2Cl_2]^+Cl^-$ to *cis*-$[Co^{III}(en)_2Cl_2]^+Cl^-$ is catalyzed by BH_4^- and similar reagents.

Even in ice-cold aqueous solutions, no evidence for a hydride was obtained[241]. Exchange experiments with ^{36}Cl showed that only one of the chloride ligands is involved in the reaction (Scheme 19).



Scheme 19. Ox = oxidizing agent.

In 1967 *Gillard*[242] suggested a general mechanism for base hydrolysis and similar reactions of Co^{III} complexes. Application to the *trans-cis*-isomerization leads to Scheme 20.



14

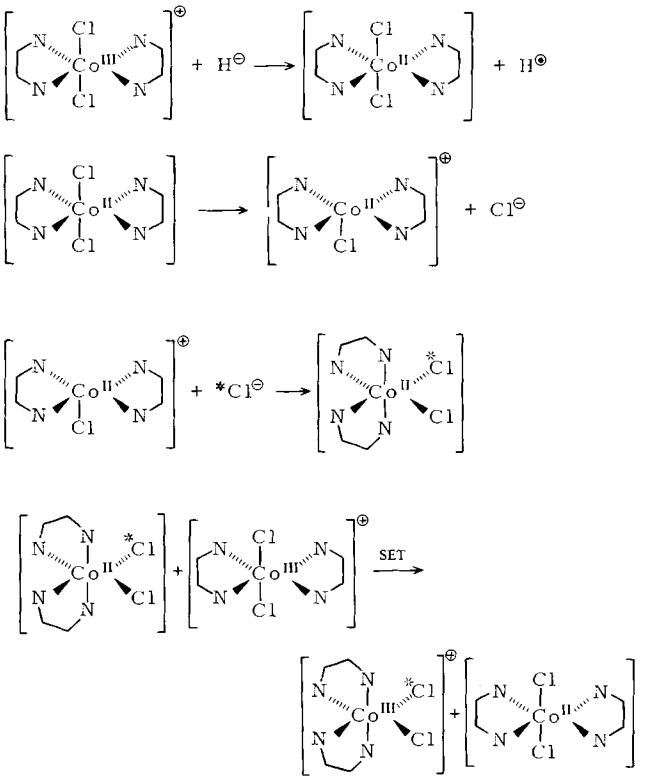
14 $\rightleftharpoons Co^{2\oplus} + 2\ en_2 + 2\ Cl^{\ominus}$

$2\ H^{\circledcirc} \rightleftharpoons H_2$

Scheme 20.

In the case of non-chelating ligands the radical pair **14** could dissociatively exchange the ligand L for X in $[Co^{III}XL_5]^{n+}$. This general mechanism was in a certain sense a precursor of the ETC S concept. However, the problem of the very rapid solvolysis of the Co^{III} ligand-bond is difficult to explain. The base may give up an electron to transform the Co^{III} complex into a highly labile Co^{II} species but it may also transform the Co^{III} complex into its conjugate base which is highly activated towards substitution[209b]. This is a very interesting aspect of the ETC concept which could find applications in the important field of acid/base catalyzed processes[243]. In any case, it was shown that the rate of hydrolysis of $[Co^{III}(NH_3)_5(NO_3)]^{2+}$ is unaffected by large amounts[244] of Cl^-, I^-, or HO_2^-, all of which are better reducing agents than OH^-; therefore, the *Gillard* mechanism (Scheme 20) was either neglected[245] or considered with some scepticism in subsequent reviews[246]. This hypothesis merits however more attention, *e.g.* by pulse radiolysis, which has already been used to measure the substitutional lability of $[Co^{II}(NH_3)_5]^{2+}$[247]. In any case, the highly polarizable hydride nucleophile seems less prone than OH^- to attack an acidic proton on nitrogen.

For these reasons we suggest as a tentative model the ETC Ra mechanism for the Co^{III} complex (Scheme 21).



Scheme 21. *Cl = ^{36}Cl.

(There is evidence that some reductions with $NaBH_4$ take place by a free radical mechanism[248]).

The observation that only one Cl ligand is exchanged requires that final single electron transfer is fast enough to prevent a second substitution of the labile Co^{II} intermediate. Other examples of ETC Ra reactions have been observed in the anodic reactions of enamines[249a], and in the cathodic reactions of azobenzenes[249b], diethyl malates or

fumarates[249c], and the diphenyl esters of thiophthalic acid[249d].

Re and Ox relate to chain reactions induced by a single electron transfer, whose overall stoichiometry correspond to a reduction[250] or an oxidation[251] of starting material. They have been repeatedly treated in reviews[252] to which the reader is referred.

The last point which should be mentioned is that intramolecular $S_{RN}1$ reactions have been described[253].

6.5.5. Principle of Redox Activation of Reactive Intermediates

The examples in this article show how a redox reagent transforms a compound into an intermediate which is able to participate in a chain reaction. We have mainly discussed reactive radical species, but there are other active intermediates[254]: carbocations[255], carbanions[104], carbenoid species[256], nitrenes[257], sulfenes[258], species with unstable oxidation states[70], highly active 1,3-dipoles[259], and substrates appropriately substituted for rapid cycloaddition[260]. These intermediates may be generated by redox reactions[261] and participate in an ETC reaction chain. The principle is not totally new[262] and has already been applied to molecular processes[263]. The ETC concept[264] should lead to a more systematic investigation of reactivity of activation processes. The variety of selective reducing[265] and oxidizing agents[266] and their combinations[267] leaves open many possibilities in this field.

7. Outlook

We close this article by apologizing to those authors whose work is relevant to the ETC concept but which we did not cite. The main reason for this is contained in Table 6 which shows the scope of this concept to date. Table 6 could also be considered as a step in improving communications between organic and inorganic chemists. In organic chemistry at present there are intensive discussions[155] to determine the relative importance of one and two electron transfers in substitutions; none of these publications cite or consider the related inorganic species[268]. The same situation prevails with the problem of associative and dissociative substitutions; the time is ripe for a more unified approach.

Between writing the first draft of this essay and publication of its final version several new papers appeared. The most relevant reviews are those on the $S_{RN}1$ mechanism[298], free-radical clocks[299], and on catalysis by electrodes[300]. The last mentioned review converges with the present essay and a more recent communication[301] to convey the message that there is indeed a class of reactions whose generality had been largely underestimated. It would seem, considering the progress in catalysis[302, 303], that the most pregnant name could be Electron Transfer Catalysis (ETC). In further reviews[303-305] we will extend the study of this new catalytic type to organometallic chemistry[304] and photochemistry[305]. $S_{RN}2$ chain mechanisms have been proposed[306] and the role of reversibility of some step on the overall selectivity[307] examined. The recently published book "Electron Transfer Reactions"[308] ignores electron transfer catalysis. A symposium on electron transfer reactions[309] is in press, and a review[310] dealing with chain substitution reaction at a C_{sp^3} atom should appear in 1982. A very important (and controversial) series of papers is expected soon: they expand the field of electron transfer mechanisms to classical electrophilic and Diels-Alder reactions[311]. The increasing number of publications in this field is reminiscent of the growth of a chain reaction.

Table 6. Application of the ETC concept. No attempt at completeness has been made; reactions of organometallic compounds of the situation of DAISET in chemical reactivity have not been considered. Some references relate to experimental results not yet interpreted within the ETC mechanism, and in some cases, the originally proposed mechanism may be the only one involved.

Compounds of	Function: Acceptor (A) Donor (D)	Oxidation State	Ref. [a]
H	A	1+	[269, 270]
	D	1−	[242, 220b]
Li	D	0	[163b]
Na	D	0	[40]
K	D	0	[271]
Cr	A	3+	[211, 171b, 272, 273]
Fe	D	0 or 2+	[226] or [251a]
	A	0	[274]
Ru	D	2+	[275-277]
Os	D	2+	[275]
Co	A	3+	[212-215]
Rh	A	3+	[86, 217-220, 278, 279]
Ir	A	3+	[216]
Pt	A	4+	[280] (cf. Section 4.1)
	D	2+	(cf. Section 5.2)
Au	A	3+	[96, 98, 99, 101]
Hg	A	2+	[45]
Tl	A	3+	[281, 80]
C	A	1+	[282] (cf. Section 2)
Si	D	1−	[123]
Ge	D	1−	[163c, 283]
Sn	D	1−	[163, 284]
N	D	3−	[285, 286]
P	D	0 or 1−	[287-290] or [291]
O	D	1−	[292, 252d]
S	D	1−	[10, 293]
Se	D	1−	[294]
Te	D	1−	[294]
Cl	D	1−	(cf. Section 4.1)
	A	0 or 1	[295] or [290, 252d]
Br	D	1−	[72, 73]
	A	0 or 1−	[296] or [297, 227c, 252d]
I	D	1−	[95]

[a] Representative literature reference and/or information.

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The Bacterial Ribosome: A Programmed Enzyme

By Hans Günter Gassen*

Ribosome-dependent protein synthesis in bacteria represents a complex sequence of reactions involving more than 150 compounds. The ribosome, constructed from 53 individual proteins and 3 nucleic acids, functions as the enzyme which catalyzes peptide bond formation. In contrast to most known enzymes the ribosome is "programmed" by the mRNA—the short-lived transcript of DNA. The ribosome reads the nucleotide message of the mRNA and transforms its information into the amino acid sequence of a protein. In the course of this process, chemical bond energy is converted into directed mechanical motion. The model of protein biosynthesis on the programmable ribosome provides answers to the following questions: how is the mRNA framed into information units, how is the substrate specificity of the ribosome modulated by the codon of the mRNA, and how does the mRNA move with respect to the ribosome by one trinucleotide per peptide bond formed?

1. Introduction**

Proteins, whose amino acid sequence corresponds in a linear fashion to the nucleotide sequence in deoxyribonucleic acid (DNA), are synthesized in all living cells on cytoplasmic particles called ribosomes. As the first step in this pathway the information of the DNA is copied onto the single stranded ribonucleic acid (RNA), mRNA. Thus, the mRNA is the short-lived programme which can be read by the ribosomes and used as information for gene encoded protein synthesis. Three nucleotides represent a codon, which is the information unit corresponding to one amino acid. The correlation between codon and amino acid is called the genetic code, which is, with a few exceptions, universal to all living beings[1].

Bacterial ribosomes are complicated particles with molecular weights (MW) of *ca.* 2.8×10^6 and are composed of 53 defined proteins and three ribonucleic acids (rRNAs). Viewed as an enzyme the ribosome catalyzes a simple chemical reaction; the conversion of an ester bond into a peptide bond. Other cellular peptide synthetases, such as the alanine-adding enzyme involved in murein synthesis, are small proteins with a MW of *ca.* 50000, but nevertheless catalyze similar reactions to the ribosome. However, the synthesis of a non mRNA-encoded polypeptide requires a multienzyme complex, in which each of the subunits is specialized in the attachment of one amino acid to the growing peptide chain[2].

In the mRNA-programmed ribosomal biosynthesis a distinctly different mechanistic principle occurs. The active center of the ribosome is modulated with respect to its substrate specificity by a defined codon, such that it can differentiate between at least 20 aminoacyl-tRNAs with high selectivity (Fig. 1). If the ribosome is viewed as a programmed enzyme the following mechanistic problems must be considered:

1) How is the start signal within the mRNA recognized and the nucleotide text framed into coding units.
2) How does the codon modulate the substrate specifity of the aminoacyl-tRNA binding site of the ribosome.
3) How is the mRNA as an "information tape" shifted by one trinucleotide per peptide bond formed.

After a basic introduction into the consecutive steps of ribosome-dependent protein synthesis and the structure of the compounds involved, an attempt is made to elucidate the mechanistic principles of the ribosome as a programmed enzyme.

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[**] *Abbreviations:* GMPPCP = Guanosine 5′-(β,γ-methylene)-triphosphate (the "triphosphate unit" bridges between P^{β} and P^{γ} *via* a CH_2 group), AcPhe-tRNA = N^{α}-acetyl-phenylalanyl-tRNA, GTPase = a phosphatase, associated with the 50S ribosomal subunit, which catalyzes the hydrolysis of GTP to GDP + P_i, N = unspecified nucleoside.

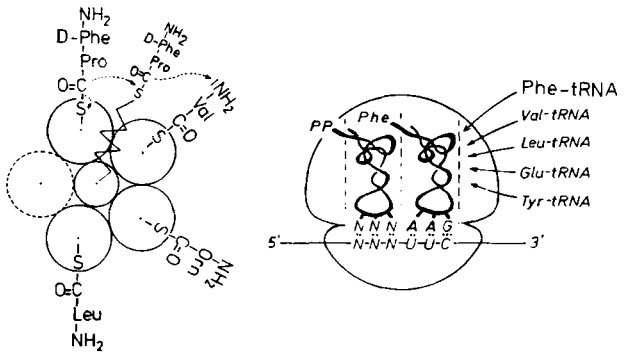

Fig. 1. Comparison of multienzyme complex displaying substrate specificity and the ribosome as a programmed enzyme.—Left: a multienzyme complex which catalyzes the synthesis of peptide antibiotics [2]. In order to explain the role of the pantetheine carrier the peptide synthetase is drawn to emphasize the similarities with the fatty acid synthetase. Right: the substrate specificity of the ribosomal aminoacyl-tRNA binding site is governed by the codon of the mRNA.

2. Bird's-Eye View of Ribosome-Dependent Protein Biosynthesis

Comparable to any other chemical or biological polymerization reaction, the biosyntheses of polypeptides can be subdivided into initiation, elongation, and termination. Each of the part-reactions is specific with respect to the compounds participating in the individual steps and the precise reaction pathway.

In the course of the initiation reaction the mRNA is framed into coding units by finding the initiator codon AUG or GUG. The initiator tRNA (fMet-tRNA$_f^{Met}$), the three initiation factors (IF-1, IF-2, and IF-3), and the small ribosomal subunit, termed the 30S subunit after its Svedberg constant, cooperate in the search for the correct start signal within the mRNA. The so-called 30S initiation complex is formed *via* a number of intermediates as depicted in Figure 2. The formation of the 30S initiation complex (30S·mRNA·(fMet-tRNA$_f^{Met}$·IF-2·GTP)·IF-1·IF-3) defines the start of a gene or a cistron. The α-amino group of the initiator tRNA has already been formylated in a non-ribosome dependent reaction: fMet-tRNA$_f^{Met}$, therefore, already carries a peptide residue that determines the direction of protein synthesis from the α-amino group to the terminal carboxyl group. Comparable to peptide synthesis by chemical means, the formylmethionine only acts as a blocking group, since the formyl group as well as the methionine residue are cleaved off in the final protein.

In the next step, the 50S subunit associates with the 30S initiation complex. In an energy-requiring reaction (hydrolysis of GTP to yield GDP + P_i), and with the concomitant release of the initiation factors IF-2·GDP, IF-1, IF3, and the so-called 70S initiation complex, 70S·mRNA·fMet·tRNA is formed: association of the two ribosomal subunits leads to formation of the aminoacyl-tRNA binding site (A site). The fMet-tRNA$_f^{Met}$ now occupies the peptidyl-tRNA binding site (P site) and an aminoacyl-tRNA may attach itself to the A site. Only the adjacent binding of two tRNA molecules to the 70S initiation complex frames the mRNA into coding units[3-5].

In the elongation cycle the aminoacyl-tRNA (AA-tRNA) in combination with its carrier protein the elongation factor EF-Tu·GTP, *i.e.* the ternary complex AA-tRNA·EF-Tu·GTP, binds to the A site of the 70S ribosome. The specificity of the A site for one defined aminoacyl-tRNA is determined by the mRNA-codon already present in the same center. The carrier protein discriminates between free tRNA and AA-tRNA, and thus prevents tRNA from binding to the A site. Both tRNAs (PP-tRNA and AA-tRNA) are now so positioned on the ribo-

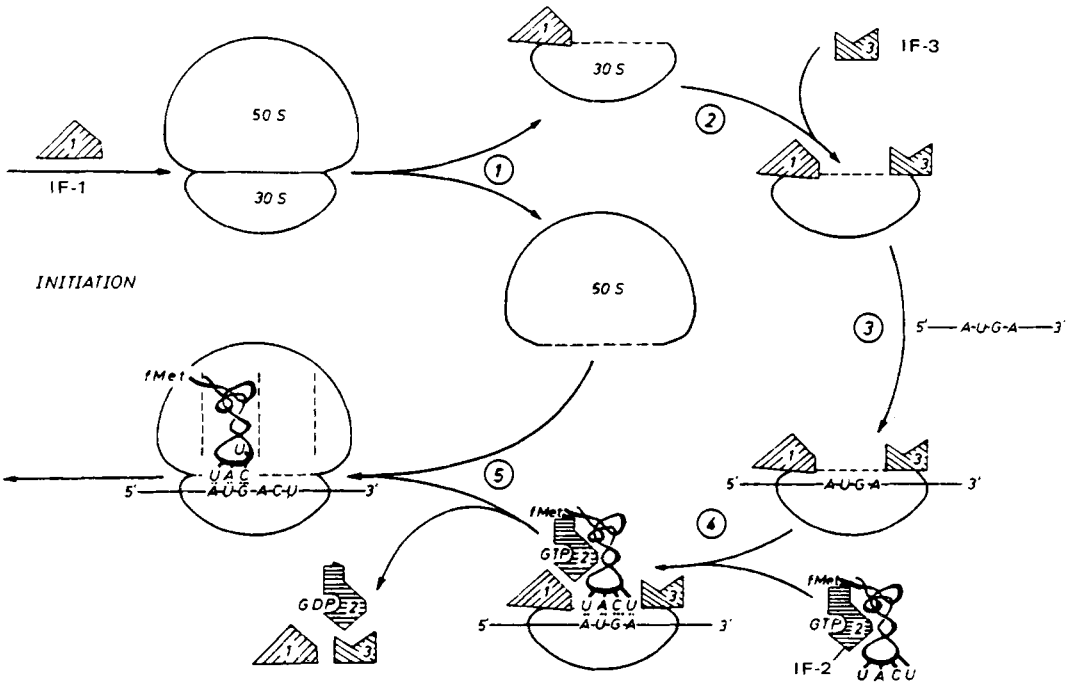

Fig. 2. Intermediate reactions in the formation of the initiation complex. ① Dissociation of the 70S ribosome into the 30S and 50S subunits; ② stabilization of the 30S subunit by the initiation factors; ③ binding of the mRNA to the small subunit; ④ formation of the 30S initiation complex; ⑤ dissociation of the factors and formation of the 70S complex. Sections 4.1 and 4.2 deal with the switch from the 30S to the 70S initiation complex in greater detail.

some that the free α-amino group of the aminoacyl-tRNA can act as a nucleophile and react with the ester bond of the neighboring fMet-tRNA$_f^{Met}$ (Fig. 3).

Prior to formation of the peptide bond *i.e.* transfer of the formylmethionine group to the aminoacyl moiety of the AA-tRNA, the elongation factor EF-Tu·GDP has to leave the ribosome. Transfer of the peptidyl moiety is catalyzed by the so-called peptidyl transferase, which is an integral part of the 50S ribosomal subunit.

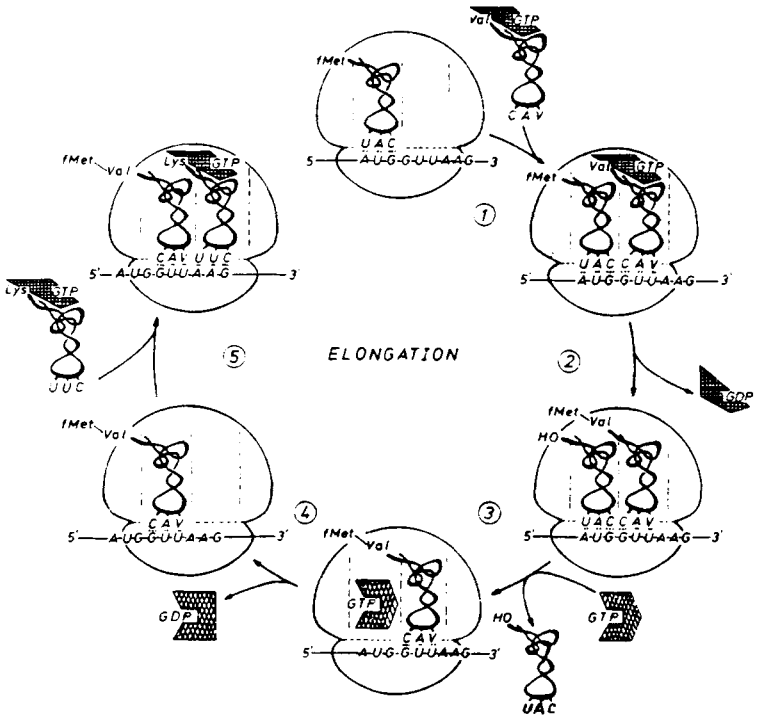

Fig. 3. The elongation cycle within the translation process. ① Binding of the ternary complex AA-tRNA·EF-Tu·GTP to the A site of a ribosome·mRNA·PP-tRNA complex; ② removal of the elongation factor EF-Tu·GDP and the simultaneous transfer of the peptidyl residue (fMet-) onto the aminoacyl-tRNA; ③ exchange of the deacylated tRNA from the P site for the elongation factor EF-G·GTP; ④ release of EF-G·GDP and the synchronous translocation of the mRNA·PP-tRNA complex; ⑤ binding of a new aminoacyl-tRNA to the now vacant A site to complete the cycle (V = modified uridine).

After transfer of the peptidyl group, a deacylated tRNA remains in the P site and the resulting peptidyl-tRNA (PP-tRNA) occupies the A site. The next step is the translocation: Catalyzed by the second elongation factor EF-G·GTP, the deacylated tRNA is removed from the P site. The peptidyl-tRNA now diffuses from the A site to the P site and a further ternary complex AA-tRNA·EF-Tu·GTP binds to the vacant A site. This series of reactions occurs once per peptide bond formed. It is terminated, when a termination codon reaches the A site of the ribosome[6–8].

In contrast to the initiation phase of translation, no termination tRNA exists for the recognition of the three termination codons UAA, UGA, and UAG. One or two termination signals in tandem are recognized by a class of proteins called termination or release factors (RF-1, RF-2, and RF-3). In cooperation with the peptidyl transferase the release factors activate a water molecule which then hydrolyzes the peptide from the tRNA (Fig. 4). After removal of the tRNA from the P site, the initiation factors IF-1 and

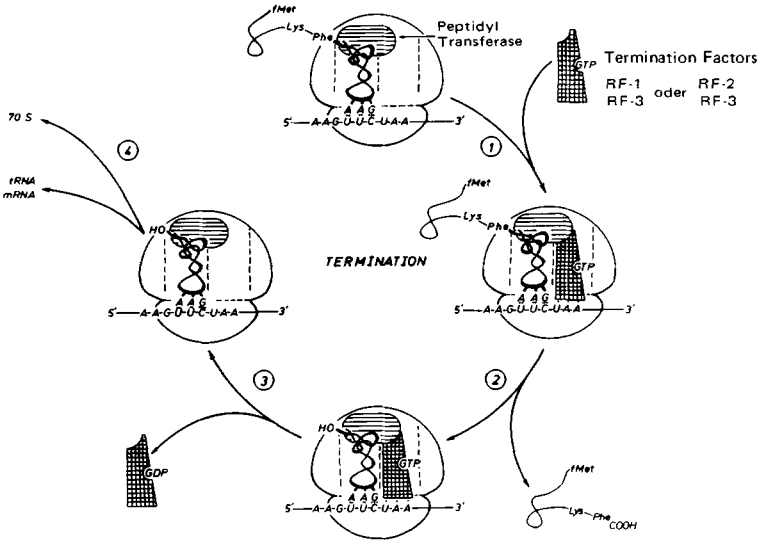

Fig. 4. Termination of peptide synthesis. ① Binding of the termination ("release") factors to the ribosome. Association of the RF-3 with the ribosome is mediated by GTP. The role of the release factors is not specified, since their molecular function is still far from being understood; ② hydrolytic release of the peptide from the tRNA. The water molecule is activated by the cooperative action of the release factors and the peptidyl transferase; ③ dissociation of the release factors accompanied by GTP hydrolysis; ④ dissociation of all components involved in peptide bond formation.

IF-3 dissociate the 70S ribosome into its subunits[9, 10]. The 30S subunit made available can then translate a new mRNA molecule into a protein.

3. Structure and Function of the Ribosomal Machinery

3.1. Ribosomes

Ribosomes have many functions. As described in Section 2 they supply the binding centers for the mRNA, the different protein factors, and the tRNA. They also create a non-aqueous microspace, enhance the catalytic activities of the factors, and display enzymic activity themselves (Fig. 5)[11].

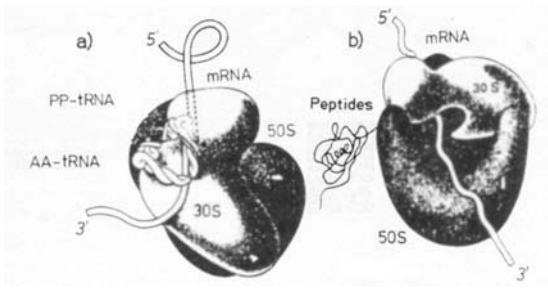

Fig. 5. Schematic representation of the binding of the tRNA and the mRNA to the ribosome.—Part a) illustrates the dimensions of both the ribosome and the tRNA. The binding domain for the AA-tRNA should be easily accessible in order to facilitate the selection of the correct AA-tRNA. The P site, however, could by buried inside the ribosome. In part b) a model for the channeling of the mRNA through the interface formed by both subunits is given. This arrangements reduces mRNA movement to an one dimensional motion. The differences in the shape of the ribosomes are explained in the legend to Fig. 6.

Bacterial 70S ribosomes are nucleic acid-protein complexes with a molecular weight of *ca.* 2.8×10^6. Following translation of the mRNA, the ribosome dissociate into two, non-identical subunits which are referred to as 30S and 50S. This dissociation occurs *in vitro* at $[Mg^{2+}] < 5$ mM. The 50S subunit (MW 1.8×10^6) contains 32 different proteins, whose molecular weights range from 8000 to 34000. They are designated L1 to L32 (L stands for large subunit). With the exception of the proteins L7 and L12, which differ only by the acetylation of their *N*-terminal amino acid, all other 50S proteins show no extended stretches of sequence homologies[12]. The 50S subunit contains two nucleic acids, 23S RNA with 2904 nucleotides and 5S RNA with 120 nucleotides[13]. The 30S subunit is constructed from 21 discrete proteins (S1—S21, S stands for small, MW 8000—64000). Protein S6 occurs in two copies within the 30S subunits, and S20, an interface protein, is identical to L26. The nucleic acid constituent—16S RNA—contains 1541 nucleotides[14, 15].

Ribosomes are spherical particles with a diameter of *ca.* 20 nm. The interpretation of pictures obtained by electron microscopy has produced different models for ribosomal shape. Three of the current models are shown in Figure 6[16–18]. The position of individual ribosomal proteins on the surface of both subparticles has been determined by immune electron microscopy[19, 20]. With the exception of protein S4, all ribosomal proteins contain an antigenic determinant, which means that parts of their structures are exposed to the surface[21]. As shown by small angle X-ray diffraction the nucleic acids form the core of each subparticle. The proteins, which are partly globular and partly elongated, form the outer layer of the nucleic acid-protein complex[22].

Fig. 6. Three-dimensional structure of 70S ribosomes and their subunits: shaded particle shows the 30S subunit. The three different models serve to illustrate the breadth of interpretations which are possible with electron microscopic images [16—18].

Using chemical methods, such as nucleic acid-specific reagents, or affinity labeling, it has been demonstrated that besides the proteins, segments of the nucleic acids are located on the surface of the ribosome. These parts of the ribosomal RNAs participate in the binding of the different substrates to the ribosome[23]. Furthermore, they are responsible for the polyanionic behavior of ribosomal particles.

The ribosomal proteins and nucleic acids are held together by electrostatic forces, hydrogen bonds, and hydrophobic interactions; covalent bonds have not been detected. Increasing the ionic strength and lowering the Mg^{2+} concentration in the medium causes a number of proteins to dissociate from the subparticles. Complete dissociation of the ribosome is achieved in 7 M urea and 4 M LiCl. From the highly purified proteins and nucleic acids isolated, active ribosomal particles can be reconstituted[24, 25].

Immune electron microscopy, affinity labeling and cross-linking were used to localize functional domains on the ribosome. With the aid of these techniques the approximate positions of the A and the P site, the peptidyl transferase center, and the binding sites of many antibiotics have been mapped (Table 1)[26].

Table 1. Localization of functional domains of the ribosome by affinity labeling. The substrates, - tRNA, antibiotics etc. - are functionalized by either chemical alkylation or by photosensitive (aromatic azides) groups[23]. The modified proteins are identified by two-dimensional gel electrophoresis or by immune precipitation. With one or two exceptions it was not possible to locate the exact nucleotide within the rRNA sequence which was modified by the affinity reagent.

Component	modified Protein or rRNA
Puromycin [a]	L23
Chloramphenicol [a]	L2, L16, L27
$tRNA_f^{Met}$	L2, L27, 23S RNA
Phe-$tRNA^{Phe}$	L2, L18, L27, S18, 23S RNA
mRNA and analogues	S1, S3, S4, S12, S18, 16S RNA
GTPase center	L2, L16, L27

[a] Both antibiotics bind to the peptidyl transferase center.

The small ribosomal (30S) subunit can bind one tRNA in the presence of mRNA, whereas the 50S subunit associates with one tRNA molecule regardless of the presence of mRNA. Programmed 70S ribosomes, however, can bind two tRNAs. At Mg^{2+} concentrations > 20 mM the binding of the tRNAs becomes independent of the mRNA. Two factors determine the substrate specificity of the tRNA binding sites. The peptidyl group directs the peptidyl-tRNA preferentially to the P site, whereas the ternary complex AA-tRNA·EF-Tu·GTP binds exclusively to the A site. The initiator tRNA·fMet-$tRNA_f^{Met}$ can only occupy the P site, and the $tRNA_f^{Met}$ by virtue of its conformation can discriminate between A and P sites (Fig. 7)[27].

A lengthy and intensive discussion has dealt with the question of whether the ribosome represents a multienzyme complex or whether the peptidyl transferase provides the sole enzymic activity of the particle. With the peptidyl transferase the term enzyme is put on trial. Peptide bond formation is not catalyzed by an individual protein, but by an as yet undetermined number of 50S proteins and segments of the nucleic acids which constitute the peptidyl transferase center[28]. It is not known at present whether the 5S RNA and 23S RNA only determine the active conformation of the proteins or if they participate in catalysis.

The GTPases represent further candidates for ribosomal enzymes. They hydrolyze the GTP within IF-2·GTP, EF-Tu·GTP, and EF-G·GTP to the respective factor·GDP complex and inorganic phosphate. Two concepts of GTP-hydrolysis are under discussion at present. On the one hand it is believed that the GTPases are integrated functions of the ribosome. Other experiments, however, can be so interpreted that the factors themselves have a latent activity which becomes apparent when these proteins associate with the ribosomes. In the presence of the antibiotic kirromycin the elongation factor Tu shows a GTPase activity which is otherwise only apparent when the factor is associated with the ribosome[29, 30].

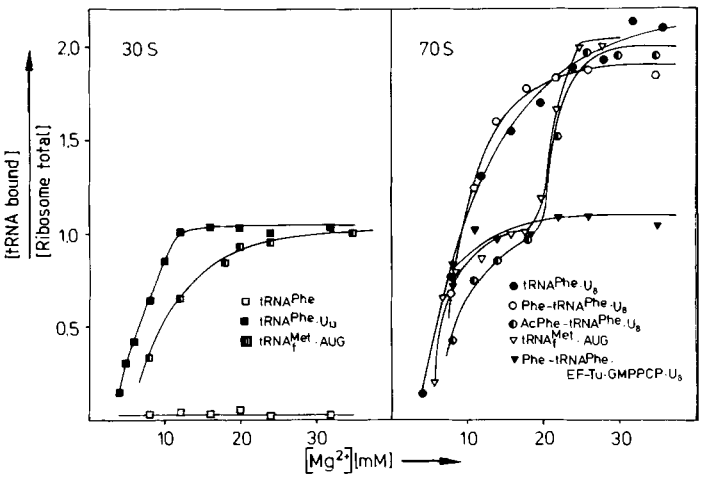

Fig. 7. Binding of different tRNAs to the ribosome.—The binding of aminoacyl-tRNA, peptidyl-tRNA, and tRNA to either 70S or 30S ribosomes was investigated by velocity sedimentation in the analytical ultracentrifuge [88]. The free tRNA boundaries were compared in the absence and presence of ribosomes. Programmed 30S subunits bind one tRNA molecule, whereas tRNA is not associated with the small subunit in the absence of the mRNA. At $[Mg^{2+}] > 20$ mM two $tRNA^{Phe}$ or Phe-$tRNA^{Phe}$ molecules bind to the 70S ribosome. Peptidyl-tRNA (AcPhe-tRNA) and $tRNA_f^{Met}$ preferentially bind to one ribosomal site at $[Mg^{2+}] \approx 15$ mM (P site). Regardless of the $[Mg^{2+}]$ only one molecule of Phe-tRNA·EF-Tu·GMPPCP can be attached to the ribosome. GTP has to be replaced by GMPPCP in this experiment to avoid hydrolysis of GTP by a ribosome-owned GTPase which would result in subsequent removal of the EF-Tu·GDP. U_8 is an octanucleotide consisting of only uridylic acid.

Comparable to other multienzyme complexes, two structural concepts have been discussed for the ribosome. In one of them the ribosome is viewed as a rigid particle which acts as a solid phase for peptide synthesis. The other model postulates a dynamic ribosome which underlies ligand-induced structural changes. These modulations of the ribosome's conformation should positively influence the rate of individual reactions within protein synthesis. Recent experimental results, such as the Mg^{2+}-dependent activation of the 30S subunit, or differences in the ^{125}iodine labeling of proteins in different functional states of the ribosome point towards a structural flexibility of the ribosome[31,32].

3.2. Transfer Ribonucleic Acids

Transfer ribonucleic acids (tRNAs) are the connecting link between the mRNA involved in the transportation of information and the proteins, multifunctional entities in living beings. Their structures also represent hybrids of nucleic acids and proteins. They contain up to 20 modified nucleosides and possess a highly complicated tertiary structure[33–35]. Within the translation process we can differentiate between four types of tRNA: initiator tRNA, aminoacyl(AA)-tRNA, peptidyl(PP)-tRNA, and deacylated tRNA. The first two only exist in their carrier-bound form, whereas PP-tRNA is always associated with ribosomes. Apart from $fMet\text{-}tRNA_f^{Met}$, peptidyl-tRNA is formed on the ribosome by the peptidyl transferase and is the substrate for the translocation process. Deacylated tRNA represents the product of the P site of the ribosome, and is removed from the ribosome by the elongation factor G under GTP hydrolysis.

The primary sequences of 120—130 tRNAs are known. With the exception of some tRNAs isolated from mitochondria, their secondary structures can be arranged in the so-called "clover leaf secondary structure"[36]. The tertiary structures of phenylalanine tRNA from yeast and of the initiator tRNA from *E. coli* have been determined by X-ray analysis in the solid state[37–39]. tRNA forms an L-shaped molecule composed of two helices positioned at right angles to one another (Fig. 8). The longer helix terminates in the single stranded anticodon loop, the shorter one in the unpaired CCA 3′-terminus. The remaining parts of both helices, designated as the dehydrouridine loop and the TΨCG-loop (Ψ signifies pseudouridine), form a functional domain which is stabilized by tertiary hydrogen bonds. It is possible that this part of the tRNA is involved in binding to the 50S ribosomal subunit [40].

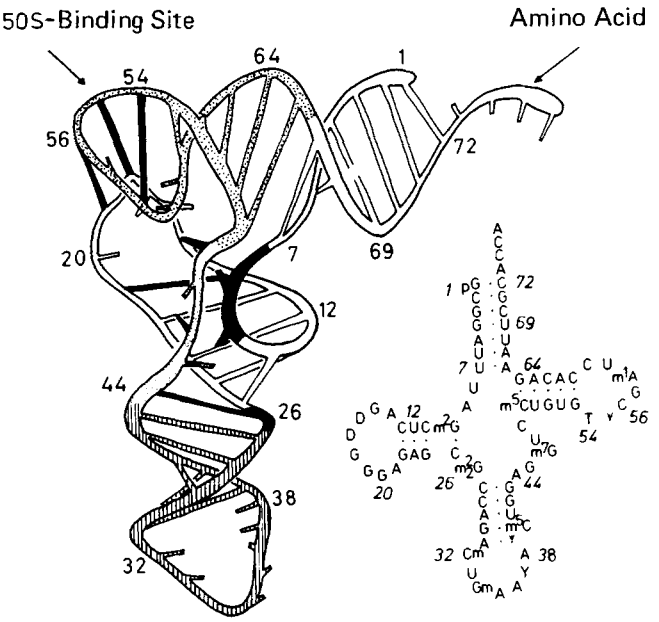

Fig. 8. Clover leaf model and tertiary structure of $tRNA^{Phe}$ from yeast. Right: the sequence of $tRNA^{Phe}$ arranged in the clover leaf form. Left: the three-dimensional structure determined by *Quigley et al.* [38]. The numerical order of the nucleotides is given to facilitate comparison between the secondary and tertiary structures.

When a tRNA binds to a mRNA programmed ribosome, the resulting codon-anticodon complex may be visualized as a continuation of the anticodon helix. The carrier protein EF-Tu·GTP should stabilize the single stranded CCA-end[41,42]. The solid state structure of $tRNA^{Phe}$ represents only one of the possible tRNA conformations. The solution structure of tRNA was therefore investigated with a battery of different techniques, such as tritium exchange, sedimentation velocity measurements, differential melting studies, ^{1}H- and ^{31}P-NMR spectroscopy, ESR spectroscopy, Raman spectroscopy, fluorescence spectroscopy, circular dichroism, laser light scattering, and low angle X-ray scattering[43]. Up until now most measurements have confirmed that the structure of tRNA in the crystal and in solution are the same. However, there is increasing evidence

that the structure of tRNA functioning in biochemical processes is not static, but may exist in different conformations optimized towards its specific function[44]. Conformational changes in tRNA may be induced by the aminoacyl and peptidyl moieties, the elongation factor Tu·GTP, the codon of the mRNA, and assorted mono- and divalent cations[45].

Structural transitions are not restricted to the ligand's binding domain, but the ligand may induce long-range effects similar to allosteric conformational changes found in proteins. It has been shown that complex formation between the codon and the mRNA not only influences the conformation of the anticodon region, but in addition influences the structure of the TΨC-loop 5 nm away[46,47]. CGAA, a tetranucleotide which is complementary to the TΨCG sequence in $tRNA^{Phe}$ and $tRNA^{Lys}$ associates only with the codon·tRNA complex, but not with free tRNA. In similar experiments evidence has been given that the reactivity of guanine bases towards kethoxal* is different with lysine tRNA and codon·lysine tRNA complexes[48]. We will deal with the codon as an allosteric effector of the tRNA conformation in more detail in Section 5.1.

The aminoacylation of the tRNA occurs in two steps. In the first reaction the aminoacyl adenylate is formed from the amino acid and ATP. Then the aminoacyl residue is transferred to either the 2′- or 3′-hydroxyl group of the terminal adenosine in tRNA. Both reactions are catalyzed by one enzyme, aminoacyl synthetase[49]. One enzyme is specific for one amino acid and the cognate tRNA. Within the cytoplasm, the AA-tRNA is immediately complexed with its carrier protein EF-Tu·GTP to avoid deacylation of the aminoacyl residue from the tRNA. The ternary complex AA-tRNA·EF-Tu·GTP represents the substrate for the aminoacyl site of the ribosome. Only AA-tRNA can form a complex with the elongation factor Tu, which prevents tRNA from blocking the A site of the ribosome[50]. In this sense tRNA can be visualized as a coenzyme which transports the aminoacyl residue and can function only when coexisting with its apoenzyme, namely elongation factor Tu·GTP.

3.3. mRNA — the Programme for the Biosynthesis of Proteins

The transcription of the mRNA from the DNA template and the translation of the template occur in bacteria in a concerted process. As soon as the 5′-end of the mRNA comes off the RNA polymerase it is occupied by ribosomes and the protein synthesis starts. Many ribosomes translate one mRNA strand simultaneously. The polysomes thus formed increase the efficiency of translation and furthermore protect the mRNA against degradation by cytoplasmatic nucleases. Prokaryotic mRNAs are mostly polycistronic, *i.e.* the information for a number of proteins is stored within one mRNA strand. Functionally, the mRNA may be subdivided into the precistronic sequence, the structural gene, the intercistronic sequence, the second and further structural genes, and the 3′-terminal sequence. The structural gene itself may be further subdivided into the initiator codons AUG or GUG, the elongation codons, and the termination codons UAA, UGA, and UAG (Fig. 9). The correlation between the mRNA codons and the individual amino acids is called the genetic code.

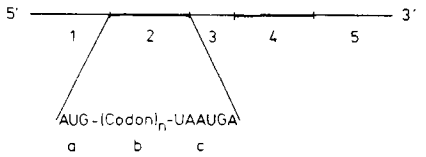

Fig. 9. Schematic representation of a polycistronic mRNA containing two cistrons. The cistronic regions containing the structural genes are indicated by a heavy line. The first cistron (gene) is subdivided into a) the initiator codon, b) the elongation codons and c) two termination codons. 1) Precistronic sequence; 2) first cistron (gene); 3) intercistronic sequence; 4) second cistron; 5) 3′-terminal sequence.

The stable interaction between the mRNA and both the 30S subunits and the 70S ribosomes depends on the Mg^{2+} concentration[51]. The nucleotide sequence in the precistronic region of mRNA is important for its association to the 30S ribosomal subunit. However, in the 70S ribosome the tRNAs regulate the stability of the mRNA·ribosome complex. At present very little is known about the molecular details of the mRNA·ribosome interaction. Since both partners are of polyanionic nature, Mg^{2+} may act as a chelating agent to bridge the negative charges of the phosphodiester bonds from both the rRNA and the mRNA. In addition, the carboxylate group from the ribosomal proteins may participate in this reaction[52].

3.4. The Factors: Proteins which Function as Enzymes, as Carriers, and as Modulators of tRNA Conformation

A number of proteins that catalyze individual steps in the translation cycle associate only temporarily with the ribosome. According to their function they are subdivided into initiation, elongation, and termination factors. The use of the term "factor" is evidence of our limited knowledge of the precise function of these proteins. The elongation factor Tu for example may act as a GTPase, represents the carrier protein for AA-tRNA, and possibly modulates the conformation of the tRNA.

The physical and biochemical properties of these factors are summarized in Table 2. In the following we deal particularly with the initiation factor 2 and both elongation factors Tu and G. IF-2·GTP and EF-Tu·GTP serve as carrier proteins for the initiator and the elongator tRNA, whereas EF-G·GTP functions as "tRNA release protein." As a common feature the three factors use GTP as an energy source to increase the speed and fidelity of protein synthesis. GTP binds to the factor and transforms it into an entity with a high affinity for either the tRNA or the ribosome. The complexes $fMet\text{-}tRNA_f^{Met}$ · IF- GTP, AA-tRNA·EF-Tu·GTP, and EF-G·GTP bind to the ribosome and fulfill their defined function. GTP is hydrolyzed to GDP by either a ribosome-owned GTPase or by the factor itself (EF-Tu), and the factor·GDP complex or the free protein

[*] 3-ethoxy-1,1-dihydroxy-2-butanone.

Table 2. Survey of the "factors" active in protein biosynthesis

Factor	MW and Cofactor	Main Function
Initiation		
IF-1	9000	Catalyzes 70S dissociation, stimulates the IF-2-and IF-3-functions
IF-2	115000, GTP	Carrier protein for fMet-tRNA$_f^{Met}$
IF-3	21000	mRNA-binding, dissociation of 70S ribosomes in 30S and 50S subunits
Elongation		
EF-Tu [a]	44000, GTP	Carrier protein for AA-tRNA
EF-Ts [a]	30000	Regenerates EF-Tu·GTP
EF-G [a]	80000, GTP (not tightly associated)	Translocation factor, release protein for the tRNA from the P site
Termination		
RF-1	44000	Terminates with UAA and UAG
RF-2	47000	Terminates with UAA and UGA
RF-3	46000, GTP	Activates RF-1 and RF-2, codon-independent

[a] The abbreviations Tu, Ts and G signify "temperature unstable", "temperature stable", and "GTP-cleavage", respectively.

leaves the ribosome. Reloading the factor with GTP occurs either through a high excess of GTP or by catalysis through a second protein. As an aid in understanding these complicated processes, the role of the elongation factor Tu is outlined in Figure 10[53]. IF-2·GTP and EF-Tu·GTP both modulatate the tRNA conformation. The function of the initiator factor 2 in the adjustment of the anticodon of fMet-tRNA$_f^{Met}$ is detailed in Section 4.1.

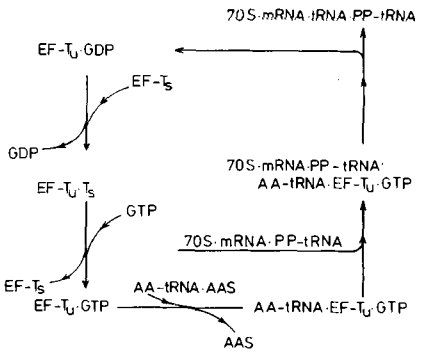

Fig. 10. Regeneration of the elongation factor EF-Tu·GTP. The scheme is to be read in a counterclockwise sense. The elongation factor Tu when activated by GTP can accept the AA-tRNA from the aminoacyl synthetase (AAS). The factor positions the aminoacyl-tRNA into the A site of the ribosome. Upon hydrolysis of GTP to GDP the factor leaves the ribosome as the EF-Tu·GDP complex. GDP is removed by the elongation factor Ts, since it has a 10-fold higher affinity compared to GTP towards EF-Tu ($K_{A_{ss}} = 2 \times 10^8\ M^{-1}$). The EF-Tu·GTP complex can be regenerated from the EF-Tu·EF-Ts dimer.

3.5. Function of Mg^{2+} Ions in Protein Biosynthesis

mRNA-dependent protein synthesis shows a distinct optimum at a Mg^{2+} concentration of 12—14 mM in cell-free systems (Fig. 11), whereas it is estimated that the Mg^{2+} concentration is 5 mM *in vivo*[54,55]. The bell-shaped curve can be subdivided into the Mg^{2+}-dependent association of the ternary complex AA-tRNA·EF-Tu·GTP and the inhibition of tRNA release from the P site by increased Mg^{2+} contrations. At $[Mg^{2+}] > 20$ mM the binding of the AA-tRNA reaches its plateau level, whilst becoming independent of mRNA. This indicates, that at high $[Mg^{2+}]$ the selectivity of the A site for a specific tRNA is lost. Likewise,

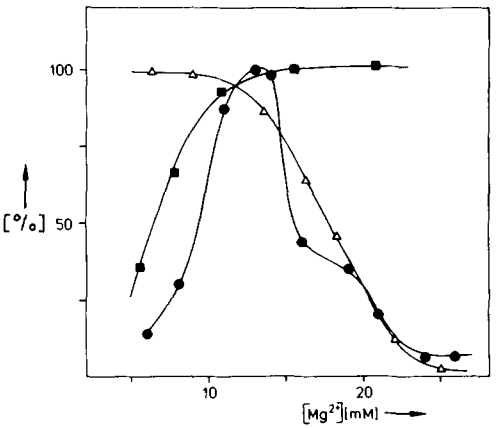

Fig. 11. Mg^{2+} dependance of the *in vitro* protein synthesis. ● Poly(Phe) synthesized; ■ Phe-tRNA·EF-Tu·GTP bound; △ $tRNA^{Phe}$ released. Poly(U) dependent ribosomal synthesis of poly(Phe) proceeds optimally at Mg^{2+} concentrations of 12—14 mM. The ascending slope of the bell shaped curve represents the Mg^{2+} dependent binding of the ternary complex AA-tRNA·EF-Tu·GTP to the ribosome. The descending slope can be explained by the effect of Mg^{2+} ions on the EF-G·GTP catalyzed release of deacylated tRNA from the P site. At $[Mg^{2+}] = 10$ mM the tRNA can be completely discharged from the ribosome by EF-G·GTP. At $[Mg^{2+}] > 25$ mM, tRNA release is blocked.

nearly all the individual steps in protein synthesis, such as the association of the mRNA to the ribosome, are Mg^{2+}-dependent. Furthermore, Mg^{2+} influences the conformation of the ribosome, the mRNA, and the tRNA. Factors and Mg^{2+} ions always act cooperatively.

Besides Mg^{2+}, the cytoplasm of bacteria contains high concentrations of polyamines such as putrescine, spermine, and spermidine. Recently it was shown by *Kurland et al.*[56] that these polyamines, as well as Ca^{2+}, increase the effectivity and fidelity of protein synthesis.

4. Selection of the Beginning of a Gene and Framing the mRNA by Formation of the Initiation Complex

During the replication and transcription processes, information is transmitted by complementary bases. Adenine pairs with thymine (uracil), and guanine recognizes cytosine and *vice versa*. However, to transform the information stored within the mRNA into the amino acid sequence of a protein three nucleotides have to be framed into a coding unit, a trinucleotide, or a codon. A framing incorrect by only one nucleotide results in a completely different amino acid sequence and such "frame shifts" are usually lethal to the cell. Therefore, cells have to be very careful in the formation of the 30S and 70S initiation complex. In a two-step procedure the 30S initiation complex selects the initiation signal AUG or GUG on the mRNA and the framing of the mRNA into coding units is achieved by formation of the 70S initiation complex.

4.1. Recognition of the Start Signal by Formation of the 30S Initiation Complex

The initiation codon AUG is selected *via* formation of the 30S initiation complex, and simultaneously the setting of the reading frame is started. One major element in the selection of the initiator codon AUG is brought about by the double strand formation between the codon of the mRNA and the anticodon of the tRNA. However, AUG is not only the initiator codon since when it occurs in the middle of a mRNA chain it also decodes methionine. Therefore, complex formation between AUG and fMet-$tRNA_f^{Met}$ cannot sufficiently explain the precision in the recognition of the beginning of a gene[57]. With bacteria the situation is even more complex. Procaryotic mRNA is polycistronic and the proteins encoded on one mRNA strand are made in varying amounts. The mRNA of the phage MS2 contains the information for the synthesis of four proteins namely maturation protein, coat protein, lysis protein, and replicase[58]. The coat protein is made in copy numbers far exceeding the remaining three proteins, in spite of the fact that its gene is located in the middle of the genome. There is only one feasible explanation for this phenomenon: the ribosome can differentiate between the initiator codons of a polycistronic mRNA. It must, therefore, be explained how the initiation system differentiates between initiator AUG and elongator AUG, and between multiple start codons within a mRNA (Fig. 12).

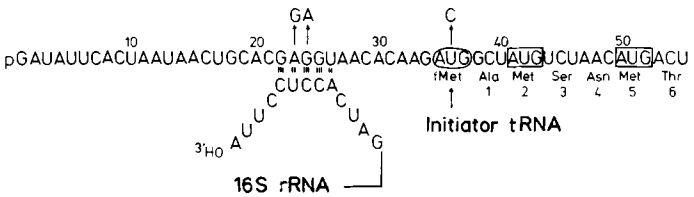

Fig. 12. Initiator sequence of the mRNA coding for a protein of the T7 phage. The sequence contains three AUG codons in the starting region of the mRNA. The initiator AUG (encircled) is followed by two elongator AUGs (boxed), which decode methionine. This demonstrates the problems in the selection of the initiator codon. The double strand formation between the 3'-end of 16S RNA and the precistronic region 7–10 nucleotides upstream of the AUG guarantees the selection of the proper AUG. Point mutations in this region or in the initiator codon reduce the efficiency of initiation complex formation [57].

At present, three explanations exist for the preferential recognition of one start codon: 1) mRNAs have a defined tertiary structure, which exposes only the initiator codon[59]. 2) mRNAs contain in their precistronic region a nucleotide sequence which is complementary to the 16S RNA of the 30S subunit. 3) The initiator tRNA may bind to more than three nucleotides of the mRNA.

In the following we will deal with theories mentioned under 2 and 3 above, since they shed some light on the mechanism of the initiation reaction.

When *Shine* and *Dalgarno* sequenced the 3'-end of the 16S RNA, they pointed out that this part of the rRNA was complementary to the precistronic region of some mRNAs. They postulated that the double strand formed between mRNA and rRNA should stabilize the ribosome·mRNA complex[60]. We now know the partial sequences (ribosomal binding sites) of *ca.* 100 mRNAs and analysis of their precistronic regions confirms the theory outlined by *Shine* and *Dalgarno*[61]. Three to nine nucleotides, which are seven to ten nucleotides upstream of the initiator codon, may form a double stranded RNA. The stability of an mRNA·30S complex is proportional to the number of complementary bases[62]. Oligonucleotides that may form a double strand with the 3'-end of the 16S RNA inhibit the formation of an initiation complex by up to 80%[63]. From these data it can be concluded that the 30S initiation complex is stabilized by the mRNA·rRNA complex. The number of complementary bases may have a regulatory function.

The trinucleotide code results in effective use of the information stored in the mRNA. On the other hand, the short RNA·RNA double strand only guarantees low stability for the mRNA·tRNA complexes. Since a tight interaction between the initiator tRNA and the mRNA is crucial for the correct reading of a gene, it has been discussed whether the fMet-$tRNA_f^{Met}$ can bind to more than three nucleotides within the 30S initiation complex. *Tanaguchi* and *Weissmann* were the first to present experimental evidence for this theory[64]. A mutant of the Qβ phage contains an mRNA in which one initiation sequence has been changed from *AUG*G to *AUG*A. The new start signal is more efficient in initiation compared to the wild type. A double mutation leading to AUAA can still recognize the initiator tRNA, whereas AUAG no longer functions as an initiation signal. It was postulated that the interaction between the 3'-terminal adenosine in AUGA and uridine 33 next to the anticodon in $tRNA_f^{Met}$ may further stabilize the codon-anticodon complex.

Table 3. Binding of fMet-tRNA or AcPhe-$tRNA^{Phe}$ to 30S- or 70S-ribosomes related to the codon. The percentage of ribosomes which exist as ribosome·tRNA complexes is listed. The amount of tRNA is kept constant, and the concentration of oligonucleotide is adjusted to optimal complex formation. With the two exceptions indicated, all experiments were performed in the presence of the initiation factor IF-2 and GTP. Tetranucleotides containing a 3'-terminal purine nucleoside (A, G, h^6A) are more efficient in forming a 30S initiation complex than AUG. However, AUG represents the best codon for formation of the 70S initiation complex. The lower part of the table shows that in the presence of initiation factor 2 UUCA can stimulate the binding of the "pseudo" initiator-tRNA AcPhe-tRNA. The amount of AcPhe-tRNA bound to the ribosome in the absence of IF-2·GTP is considerably lower.

Oligonucleotide	Percentage of tRNA-binding ribosomes	
	30S [%]	70S [%]
		fMet-tRNA
AUG	44	71
AUGA	72	44
AUGG	68	43
AUGU	52	63
AUGC	56	57
AUGh^6A [a]	61	47
AUUA	9	11
AUUU	0	0
AUG(−GTP)	22	—
AUG(+GMPPCP)	—	46
AUGA(−GTP)	35	—
AUGA(+GMPPCP)	—	65
		AcPhe-tRNA
UC(−IF-2, −GTP)	28	—
UUC	36	—
UUCA (−IF-2, GTP)	9	—
UUCA	47	—

[a] h^6A is deaminated in position 6 of the adenosine.

This hypothesis is supported by the known tertiary structure of the initiator tRNA. In contrast to $tRNA^{Phe}$, uridine 33 occupies an exposed position in $tRNA_f^{Met}$. There is the possibility that an additional Watson-Crick type base pair between adenosine and uridine is formed[39]. Tetranucleotides such as U*AUG* and *AUG*A, which may form a four base-paired complex with the $tRNA_f^{Met}$, are more efficient as initiation codons compared to AUG. Here, efficient means that a higher percentage of 30S ribosomal subunits can be saturated with fMet-$tRNA_f^{Met}$·IF-2·GTP in the presence of either U*AUG* or *AUG*A[65–68]. Since both neighboring nucleotides show this stimulatory effect, the pentanucleotide U*AUG*A may represent the ideal initiation sequence.

The initiation factor IF-2 plays an important role in recognition of the start signal by the initiator tRNA. Unlike the free fMet-$tRNA_f^{Met}$, the ternary complex fMet-$tRNA_f^{Met}$·IF-2·GTP prefers the tetranucleotide. If the initiator tRNA is replaced by AcPhe-tRNA—a pseudo-initiator tRNA—then the free AcPhe-tRNA prefers the codon UUC. The ternary complex AcPhe-tRNA·IF-2·GTP, however, reacts preferentially with the tetranucleotide UUCA (Table 3)[66]. IF-2·GTP alters the tertiary structure of the fMet-$tRNA_f^{Met}$ in such a way that four or five anticodon bases may interact with the start signal on the mRNA (Fig. 13).

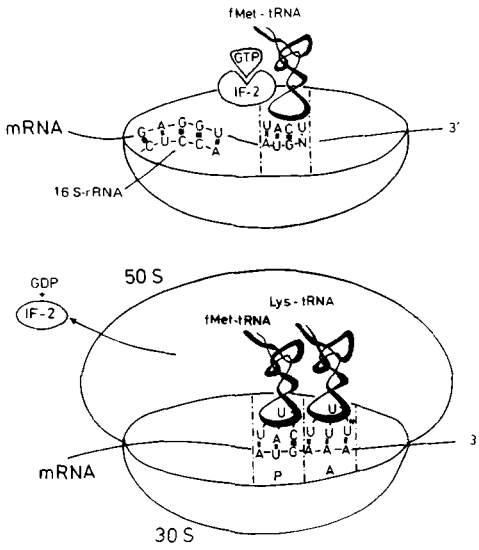

Fig. 13. Model of the 30S and 70S initiation complex. The 30S initiation complex is stabilized by the formation of two RNA·RNA double strands. The ternary complex fMet-$tRNA_f^{Met}$·IF-2·GTP can bind to more than three nucleotides of the mRNA. In the 70S initiation complex, the two tRNAs and the mRNA may form a continous hexanucleotide double strand (see Fig. 1 step 4 and 5).

In summarizing points two and three mentioned above, the high specificity in the recognition of the gene start may be explained as follows: The 30S ribosomal complex is stabilized by two RNA·double strands that are at a defined distance of about 2.5 nm from one another. The 16S RNA binds the intercistronic sequence of the mRNA and the fMet-tRNA·IF-2·GTP holds the start codon[69]. Initially, 30S ribosomal subunits and mRNA form a loose association which is stabilized by electrostatic interactions using Mg^{2+} as a chelating agent. By a "slide and search mechanism" the correct binding of the mRNA is achieved by formation of a three to nine nucleotides-long hybrid between the 16S RNA and the mRNA. However, only the second interaction between the initiator tRNA and the initiator codon results in the formation of a stable initiation complex (Fig. 13).

From an analysis of the ribosomal binding sites of more than 100 mRNAs it becomes evident that AUGA/G is always used as a start codon when the number of complementary bases in the precistronic region of the mRNA is low[61]. This could indicate, that the efficiency of initiation complex formation, *i.e.* the number of protein copies from a given mRNA, is regulated by the degree of base complementary in both the precistronic region and the initiator codon.

4.2. Final Framing of the mRNA within the 70S Initiation Complex

The addition of the 50S subunit to the 30S initiation complex results in the formation of the 70S initiation complex. GTP is hydrolyzed to GDP and inorganic phosphate, and IF-2·GDP leaves the ribosome. The free fMet-$tRNA_f^{Met}$ occupies the P site and now represents a peptidyl-tRNA.

The second tRNA binding site, specific for the aminoacyl-tRNA is now formed. However, before a second tRNA can be bound next to the fMet-$tRNA_f^{Met}$, the postulated tetranucleotide complex between the fMet-$tRNA_f^{Met}$ and the mRNA has to be reduced to the normal trinucleotide code. Only by formation of 70S·mRNA·PP-tRNA·AA-tRNA is the framing of the mRNA to trinucleotide coding units achieved.

In order to understand the switch from the tetranucleotide code in initiation to the trinucleotide code in elongation at a molecular level we investigated the function of the initiation factor IF-2 (Table 3). The ternary complex fMet-$tRNA_f^{Met}$·IF-2·GTP binds with preference to *AUGA* or *AUGG* programmed 30S subunits. However, with 70S ribosomes AUG is more effective in the binding of the fMet-$tRNA_f^{Met}$ compared to *AUGA* or *AUGG*. The dissociation of the initiation factor IF-2 from the 70S ribosome can be prevented by replacing GTP with the non-cleavable analogue GMPPCP. Under these experimental conditions, *i.e.* the existence of a fMet-$tRNA_f^{Met}$·IF-2·GMPPCP complex on the 70S ribosome, the tetranucleotide *AUGA* is again the better codon compared to AUG. Furthermore, the presence of IF-2·GMPPCP on the 70S ribosome blocks the binding of aminoacyl-tRNA to the A site.

The carrier protein IF-2·GTP of the fMet-$tRNA_f^{Met}$ adjusts its conformation such that the initiator tRNA may bind to more than three nucleotides on the mRNA (Fig. 13). In the 70S ribosome, however, by necessity of the elongation process interaction between the tRNA and the mRNA has to be reduced to the trinucleotide code. A ribosomal GTPase hydrolyzes GTP and the resulting binary complex IF-2·GDP leaves the ribosome. The binding of fMet-$tRNA_f^{Met}$ to the 70S ribosome should now be additionally stabilized by interaction between the "peptidyl" group and components of the 50S subunit[70]. As soon as the first complex, AA-tRNA·EF-Tu·GTP, binds to the A site of the ribosome the framing of the mRNA is guaranteed.

5. Peptide Chain Elongation in Protein Biosynthesis: Modulation of Substrate Specificity and the Transport of the Programme

Two aspects of the elongation cycle in ribosomal protein biosynthesis deserve special attention with regard to their mechanism: Modulation of the substrate specifity of the A site for the different aminoacyl-tRNAs by the mRNA codon, and the GTP-dependent translocation of the mRNA by one codon per peptide bond formed.

5.1. The Selection of a Cognate Aminoacyl-tRNA by a Programmed 70S Ribosome

The ternary complex AA-tRNA·EF-Tu·GTP binds to a 70S ribosome which contains a peptidyl-tRNA in the P site and a free mRNA codon in the A site. The "A site" binding domain, by virtue of its protein and nucleic acid composition, guarantees stable binding of the aminoacyl-tRNA ($K_{Ass} \approx 10^8$ M^{-1} at [Mg^{2+}] > 20 mM). On the other hand, the codon determines the selective capacity of the A site, *i.e.* which of the 50—100 different AA-tRNAs becomes associated with the A site[71]. The selection of the cognate tRNA depends not only on the three anticodon bases, but also on the neighboring nucleotides of the anticodon. In addition, the 16S RNA and proteins located in the decoding domain also contribute to the selectivity[72].

Initially, the selection of the correct AA-tRNA was explained by formation of a trinucleotide double strand between the codon of the mRNA and the anticodon of the tRNA. This assumption, however, is not sufficient to explain the low error frequency of 10^{-4}. Trinucleotides with complementary bases do not form dimers in aqueous solution, and complex formation between a tRNA and a cognate trinucleotide is only of low stability ($K_{Ass} \approx 10^3 - 10^4$ M^{-1})[73,74]. If the trinucleotide is replaced by a second tRNA whose anticodon is complementary to the first tRNA, *i.e.* $tRNA^{Phe}$ (UUC) and $tRNA^{Glu}$ (GAA), then stable tRNA dimers are formed with association constants in the range of 10^6 M^{-1}[75]. The association rate constants of oligonucleotide·tRNA complexes are comparable with those of tRNA dimers, whereas the dissociation rate constants of the dimeric tRNA are slower by a factor of 10^6 ($k_{Diss} \approx 5$ s^{-1})[76].

Recently, a number of experiments have contributed to the understanding of correct aminoacyl-tRNA selection by the programmed A site. Using the above mentioned tRNA dimers as a model system, evidence was given that differences in the association constants between cognate (three base pairs) and non-cognate (only two base pairs) tRNA dimers result from differences in the dissociation rate constants. The association rate constants are, within small limits, the same for cognate and non-cognate dimers[77,78]. We were able to show that a codon allosterically affects the conformation of the tRNA[46]. The sequence TΨC(G,A), common to nearly all tRNAs active in ribosomal protein synthesis, is buried within the tertiary structure of tRNA. This sequence is neither accessible for chemical modification nor for the binding of complementary oligonucleotides such as CGAA (see Fig. 8). However, in the codon·tRNA complex this region of the tRNA molecule becomes accessible to both chemical reagents and for oligonucleotide binding. CGAA binds to a U_8·$tRNA^{Phe}$ complex with an association constant of 5×10^4 M^{-1}[46]. The presence of CGA increases the stability of the codon·anticodon complex by a factor of 10 (Fig. 14). Kinetic experiments performed by *Pörschke et al.* confirmed the codon-induced conformational change of the tRNA[79].

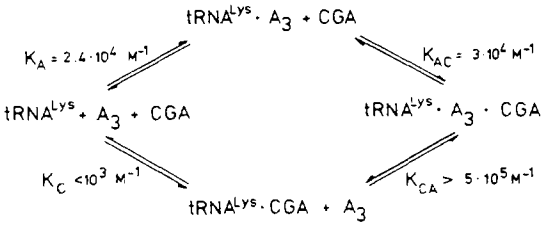

Fig. 14. Codon-induced structural transition in tRNA. Reaction scheme for the binding of A_3 and CGA to $tRNA^{Lys}$. The trinucleotide CGA binds to an $tRNA^{Lys} \cdot A_3$ complex ($K_{AC} = 3 \times 10^6$ M^{-1}) but not to free tRNA. In the presence of CGA the stability of the codon-anticodon complex is increased by a factor of 10 ($K_{CA} = 5 \times 10^5$ M^{-1}).

The TΨC(G,A) sequence, as exposed in the codon·tRNA complex, may bind to a complementary sequence within the 5S RNA (C43GAA46) or similar sequences in 16S RNA[80]. The mRNA codon acts as an allosteric effector which induces the binding type conformation of the tRNA. As a consequence of the codon-anticodon complex the conformation of the tRNA is altered such that a RNA-RNA double strand is formed between the tRNA (TΨC(G,A)), and the ribosomal RNA. This type of interaction is identical for all tRNAs, whereas the formation of the codon·anticodon complex is a selective type of reaction. Each AA-tRNA associates with the codon-programmed A site in the form of its ternary complex AA-tRNA·EF-Tu·GTP. When the codon and the anticodon of tRNA do not match, the tRNA dissociates from the A site again ($k = 10^{-5}$ s^{-1}). A matching codon-anticodon complex induces a conformational change in the tRNA that results in stable binding of the AA-tRNA to the A site. The double strand formation between the now exposed TΨC(G,A) sequence and the ribosomal RNA is part of the stable interaction. In the *in vivo* situation the AA-tRNA does not dissociate from the ribosome, but following the removal of the elongation factor EF-Tu·GDP and transfer of the peptidyl moiety as peptidyl-tRNA is translocated to the P site.

5.2. Translocation, the Energy-Dependent Movement of the mRNA with Respect to the Ribosome

Elongation is a cyclic process within protein synthesis which occurs once per peptide bond formed. A peptidyl-tRNA occupies the P site and an aminoacyl-tRNA is located in the A site. Following the dissociation of the elongation factor as EF-Tu·GDP, the peptidyl moiety is transferred to the aminoacyl group of the AA-tRNA. This reaction is thought to be catalyzed by peptidyl transferase. This state of the ribosome represents the pre-translocational state, which means that a tRNA is now in the P site and the peptidyl-tRNA occupies the A site. The consecutive trans-

location process can be subdivided into two individual steps: removal of the deacylated tRNA from the P site, and movement of the mRNA and PP-tRNA by a codon's length from the A to the P site. A peptidyl-tRNA, containing a peptidyl moiety elongated by one amino acid, is located in the P site and the neighboring A site is again free for the acceptance of a new AA-tRNA. However, the deacylated tRNA has to be removed from the P site before translocation can occur. This process requires chemical bond energy in the form of GTP, and the elongation factor EF-G·GTP replaces the tRNA in a stoichiometric exchange reaction. The data shown in Figure 15 demonstrate that the stoichiometry and the rates of the EF-G·GTP-dependent release of tRNA may be correlated with the binding of a new AA-tRNA and thus with the translocation reaction[81]. Following this, it could be said that the second elongation factor functions as the counterpart of the elongation factor Tu. The EF-G·GTP complex has a high affinity for the ribosome and acts as a tRNA release protein. At present it is not known whether factor and tRNA compete for the same binding site, or whether the elongation factor reduces the affinity of the ribosome for the tRNA in an allosteric fashion. Prior to translocation of mRNA and

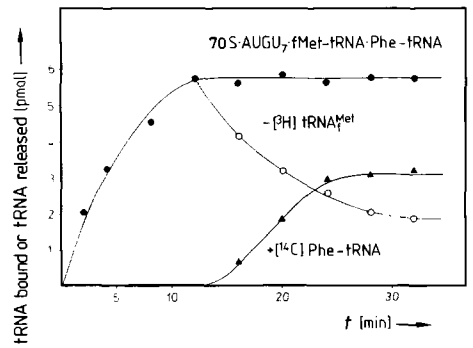

Fig. 15. Binding of an additional Phe-tRNA to the complex 70S·AUGU$_7$·fMet-tRNA·Phe-tRNA after addition of EF-G·GTP. The translocation of the PP-tRNA·mRNA complex occurs simultaneously with the EF-G·GTP-catalyzed release of tRNA. In the initial complex, an fMet[^{3}H]-tRNA$_f^{Met}$ (tritium labeled at the CCA end) occupies the P site, whereas a Phe-tRNA binds to the A site. The curve marked (●) shows the kinetics of formation of the complex 70S·AUGU$_7$·fMet-[^{3}H]tRNA·Phe-tRNA. 10 pmol 70S ribosomes were used. After 12 min, the addition of EF-G·GTP and [^{14}C]Phe-tRNA^{Phe} (labeled in the amino acid) induced the release of deacylated tRNA ([^{3}H]tRNA$_f^{Met}$ (○)) and the simultaneous formation of a new Phe-tRNA (△). This indicates that the 70S·AUGU$_7$·fMet-Phe-tRNA·Phe-tRNA complex was formed.

PP-tRNA, the factor G has to be removed from the ribosome. GTP is hydrolyzed to GDP and inorganic phosphate by a 50S subunit-owned GTPase[82]. This GTPase activity may be one of the functions of the protein pair L7/L12 which exists in duplicate on the large subunit. If GTP is replaced by the analogous GMPPCP, tRNA is still removed from the ribosome, but the factor remains associated with the ribosome, and peptide synthesis stops[34,83]. Furthermore, tRNA can be displaced from the P site by lowering the Mg^{2+} concentration from about 15 to 7 mM. Under these conditions (factor-free system), all partial reactions of the elongation cycle occur, albeit at a very low rate. The energy of the ester bond stored in AA-tRNA is sufficient to form a peptide bond. Chemical bond energy in the form of GTP is used to regulate the affinity of a tRNA release protein towards the ribosome and to increase the rate of tRNA-dissociation. With both factors, EF-Tu and EF-G·GTP, hydrolysis has to occur before the factor can be removed from the ribosome.

The movement of the peptidyl-tRNA from the A to the P site may be explained if one accepts a concept originally proposed by *Leder*[84]. The binding domain of an enzyme has a high affinity for its substrate and a reduced affinity for the resulting product. Applied to the translocation process this should mean the following. The transfer of the peptidyl moiety converts the AA-tRNA in the A site to a peptidyl-tRNA and thus to the product of the A site. The same conversion occurs at the P site, the deacylated tRNA representing the product of the P site, which is released by EF-G·GTP action. Now the neighboring P site is free and represents the high affinity site for the peptidyl-tRNA (substrate). Thus, peptidyl-tRNA should diffuse from A to P as soon as the P site is empty. Up until now it has been difficult to prove this elegant theory from quantitative experimental data. The purity of the individual components, as well as the techniques applied, *i.e.* adsorption of the complexes on nitrocellulose filters, have not allowed the exact determination of the association constants under equilibrium conditions. Previously we have shown that one can prepare 70S ribosomes that under appropriate experimental conditions will bind exactly two RNA molecules. Working in collaboration with *Riesner*, we used velocity sedimentation in the analytical ultracentrifuge to make separate determinations of the affinity constants of PP-tRNA to the A and P sites of the ribosome[27]. The respective data listed in Table 4 confirm the theory proposed by *Leder*. AcPhe-tRNA, an analogue of peptidyl-tRNA, or $(Phe)_2$-tRNA has a 20-fold higher affinity for the P compared to the A site. Thus, translocation of the peptidyl-tRNA has to be visualized as a directed diffusion reaction which occurs spontaneously as soon as the P site is free. The 20-fold difference in the association constants indicates that under equilibrium conditions both domains are occupied to an extent 95% P and 5% A. However, the reaction becomes irreversible when the ternary complex AA-tRNA·EF-Tu·GTP binds to the A site. Only this reaction guarantees the directed diffusion of the PP-tRNA from the A to the P site.

Table 4. Apparent binding constants of AA-tRNA, peptidyl-tRNA, and tRNA to programmed 70S ribosomes; number per ribosome bound.

tRNA	Number of bound tRNAs	Binding site [a]	K_{ass} [M^{-1}] [b]
Phe-tRNA·EF-Tu·GMPPCP [c]	1	A	$6.6 \cdot 10^6$
AcPhe-tRNA	1	P	$3.5 \cdot 10^6$
AcPhe-tRNA	1	A	$1.8 \cdot 10^5$
Phe-tRNA	2	A, P	—
tRNA$_f^{Met}$	1	P	$2.1 \cdot 10^5$
tRNA^{Phe}	2	A, P	—

[a] The specifity of the peptidyl-tRNA for either A or P site can be deduced from the accepted mechanism of translocation. No direct experimental evidence exists, as yet, for the site-specificity. [b] The association constants K_{ass} were calculated from the sedimentation of the complexes in the analytical ultracentrifuge at a Mg^{2+} concentration of 8 mM (see also Fig. 7). [c] Within the ternary complex Phe-tRNA·EF-Tu·GTP, GTP was replaced by the non-cleavable GMPPCP to prevent hydrolysis by 70S-GTPase.

One of the crucial questions in the translocation process left to be solved was whether the peptidyl-tRNA and the mRNA are translocated as a codon-anticodon associated unity, or whether the individual components are transported separately. This problem was answered by an elegant experiment performed by *Küchler*[85]. In the 70S·poly(U)·AcPhe-tRNA complex he crosslinked (by UV irradiation) the tRNA covalently to the polyuridylate *via* the codon and anticodon bases. The crosslinked poly(U)·AcPhe-tRNA entity translocates normally from the A to the P site, and the peptidyl group can then be transferred to puromycin. Further evidence for the translocation of a PP-tRNA·mRNA complex comes from a frame shift suppressor tRNA, which occupies four mRNA bases and moves the mRNA by four nucleotides[86a].

In order to investigate the molecular details of the translocation process we devised our experiments according to the following assumptions: Release of the deacylated tRNA from the P site, should destabilize the mRNA ribosome interaction. On the other hand, the peptidyl-tRNA should have an increased affinity for the mRNA, brought about by the tightening of the codon·anticodon complex. Therefore, we measured the binding of oligonucleotides to the ribosome as related to the presence of cognate tRNAs (Table 5). A stable interaction ($K_{Ass}=2.2\times10^{8}$ M^{-1}) between the mRNA analogues and the 70S ribosome occurs either in the presence of two cognate tRNAs or a peptidyl-tRNA[87]. With only one tRNA present the ribosome·oligonucleotide complex is of intermediate stability, a state of the ribosome which may be correlated to the pretranslocational state. From the data listed in Table 5 it is evident that the affinity of an mRNA for the ribosome is not determined by its chain length, but by the number of cognate tRNAs.

Table 5. Effect of the chain length of polyuridylic acid and cognate tRNAs on the formation of the formation of the 70S AUGU$_n$ complex [88]. The association constants were measured by equilibrium dialysis and were derived from a Scatchard plot for ten different oligonucleotide concentrations.

Complex	tRNA	K_{Ass} [M^{-1}]	Number of binding stites
70S·AUGU$_3$	–	$6.8\cdot10^{5}$	1.3
70S·AUGU$_6$	–	$8.7\cdot10^{5}$	1.3
70S·AUGU$_{13}$	–	$9.3\cdot10^{5}$	1.4
70S·AUGU$_3$	tRNA$_f^{Met}$	$4.6\cdot10^{7}$	1.0
70S·AUGU$_3$	tRNA$_m^{Met}$	$3.9\cdot10^{6}$	1.0
70S·AUGU$_3$	tRNA^{Phe}	$4.1\cdot10^{6}$	1.2
70S·AUGU$_3$	tRNA$_f^{Met}$, tRNA^{Phe}	$2.2\cdot10^{8}$	1.1
70S·AUGU$_6$	tRNA$_f^{Met}$, tRNA^{Phe}	$2.1\cdot10^{8}$	1.0
70S·AUGU$_{13}$	tRNA$_f^{Met}$, tRNA^{Phe}	$2.2\cdot10^{8}$	1.1
70S·AUGU$_3$	fMet-tRNA$_f^{Met}$	$1.1\cdot10^{8}$	1.1
70S·AUGU$_3$	AcMet-tRNA$_m^{Met}$	$5.3\cdot10^{7}$	1.1

In order to prove our second assumption we compared the association constants of a peptidyl-tRNA·oligonucleotide complex with either tRNA or aminoacyl-tRNA (Table 6). The peptidyl-tRNA, with or without ribosomes, binds a cognate oligonucleotide 3–20 times tighter than deacylated tRNA[86b]. These data further support the idea of translocation of a peptidyl-tRNA·mRNA complex.

Table 6. Effect of the peptidyl moiety on the stability of the oligonucleotide·tRNA-or ribosome·oligonucleotide-tRNA complex.

Oligonucleotide	tRNA	Ribosome	K_{Ass} [M^{-1}] [a]
AUG	tRNA$_f^{Met}$	–	$4.4\cdot10^{3}$
	fMet-tRNA	–	$1.2\cdot10^{4}$
AUGA	tRNA$_f^{Met}$	–	$4.0\cdot10^{4}$
	fMet-tRNA$_f^{Met}$	–	$1.2\cdot10^{5}$
UUC	tRNA^{Phe}	–	$1.7\cdot10^{3}$
	AcPhe-tRNA^{Phe}	–	$1.1\cdot10^{4}$
	tRNA^{Phe}	+	$6.3\cdot10^{5}$
	AcPhe-tRNA^{Phe}	+	$9.5\cdot10^{6}$
UUCA	tRNA^{Phe}	–	$3.2\cdot10^{4}$
	AcPhe-tRNA^{Phe}	–	$1.9\cdot10^{5}$
	tRNA^{Phe}	+	$2.3\cdot10^{6}$
	AcPhe-tRNA^{Phe}	+	$1.8\cdot10^{7}$

[a] Association constants were determined by equilibrium dialysis.

Translocation has to be viewed as a concerted reaction. Transfer of the peptidyl moiety from the tRNA in the P site to the AA-tRNA placed in the A site and consequent removal of the deacylated tRNA from the P site result in PP-tRNA in the A site, and an empty P site. The PP-tRNA, however, has a higher affinity for the P site and the peptidyl moiety induces a structural change within the tRNA which increases the stability of codon-anticodon interaction 5–20fold. The mRNA is primarily held in the ribosomal complex by binding to the tRNA, and hence translocation may be regarded as a shift of the PP-tRNA·mRNA from its site of low affinity to that of high affinity. Given the relevant binding constants, the shift of the PP-tRNA to the P site should only occur to an extent of 95%; however, it is driven to irreversibility by the binding of the ternary complex AA-tRNA EF-Tu·GTP to the vacant A site.

The main function of the ribosome could be to provide the specific binding sites for the components necessary for peptide bond formation and to form a cavity which prevents dilution of the PP-tRNA and the mRNA during translocation. Mechanical movement is explained as a diffusion from a low- to a high-affinity binding site. The continuous shift in one direction is guaranteed by the consecutive irreversible GTP hydrolysis. Conformational transitions of the ribosome do not seem to be necessary for this mechanism.

6. Prospects

Many details of the initiation and elongation steps in bacterial protein biosynthesis are known and it is only the mechanism of the termination reaction that remains in the dark. However, kinetic data on these processes, which should shed some light on the speed and accuracy of peptide synthesis, are still missing. This type of experiment has failed up to now, since the complexity of the systems involved does not allow the unambiguous interpretation of the experimental data. An area which shows great promise for the future is the X-ray structural analysis of ribosomal components and of the ribosome itself. Comparable to the scientific impact of the three-dimensional structure of the tRNA^{Phe}, the determination of the three-dimensional structure of the ribosome now in progress, should deepen our understanding of the molecular principles of protein-nucleic acid interaction.

It is interesting to compare facts known about bacterial synthesis with those valid for eukaryotic systems. The eukaryotic 80S ribosome consists of about 80 proteins and four nucleic acids, and thus shows a far greater complexity compared to the bacterial ribosome. The mRNA is monocistronic, starting with the cap sequence and containing a 200 nucleotide poly(A) segment at the 3'-end. The initiator tRNA is not formylated, and the seven initiator factors have a molecular weight of more than one million in total[88]. Whereas the elongation cycle and the termination reaction are similar in prokaryotes and eukaryotes, with respect to their mechanisms, the initiation process is very different in this respect. All known regulatory mechanisms work at the level of the initiation process. The initiation factor IF-2 (eIF-2), which functions as a carrier protein for Met-tRNA$_{i}^{Met}$, can be inactivated by a protein kinase catalyzed phosphorylation. The inactivation of the initiation factor is further coregulated by some interferons, 2',5'-oligo(A) synthetase, and cAMP protein kinases[89]. The mechanism of eukaryotic initiation may provide some clues on the molecular principles of cell differentiation and growth of malignant cells.

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The Chemistry of Acyl Cyanides

By Siegfried Hünig* and Rainer Schaller

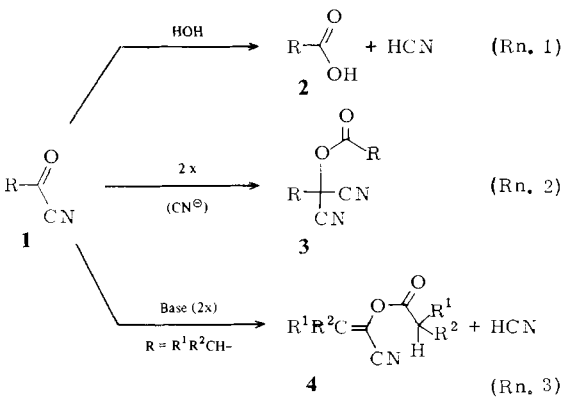
Through improved and novel syntheses, acyl cyanides—especially aliphatic acyl cyanides—have become so readily accessible that numerous synthetic applications present themselves. The present review surveys the development of the chemistry of the acyl cyanides during the last 25 years. The syntheses and most important reaction possibilities of R—CO—CN are outlined in four large schemes: reactions of the CO- and CN-groups—in each case with preservation of the carbon skeletal framework—as well as acylations with cleavage of cyanide ions.

1. Introduction

Although the first acyl cyanide had already been reported[2] as long ago as 1832, it was not until 1956 before a comprehensive review of the acyl cyanides and their chemistry appeared in the literature, by *Thesing et al.*[1]. During recent years this class of compounds has substantially gained in importance, especially as a result of new synthetic methods and their use as building blocks for heterocycles (herbicides), so that a fresh survey may be rewarding. We start deliberately from *Thesing*'s presentation, the contents of which are largely taken for granted.—A later survey of synthetic methods covers the literature up to 1974[3].

2. General Properties of Acyl Cyanides

Acyl cyanides **1** are usually colorless solids or liquids. Their infrared spectrum shows an intense and sharp CN-band at 2210—2250 cm^{-1} and a strong CO-band at 1645—1720 cm^{-1}[4], which can be used as good indicators to follow the course of a reaction. Because of their strong carbonyl activity, which can be utilized for mild acylations (Section 4.4), they are sensitive to hydrolysis **(1→2)** (Section 4.4.1). In presence of cyanide ions (hydrolysis!) "dimeric acyl cyanides" **3** are formed (Section 5). Finally, bases can convert enolizable acyl cyanides into their acylated enols **4** (Section 4.2.3).



In the synthesis of acyl cyanides, as well as in any application, their reactivity according to reactions 1—3 has to be taken into account. It is especially due to the formation of **3** and **4** that no satisfactory syntheses of aliphatic acyl cyanides have existed until recently. For the same reason it was only lately that a series of consecutive reactions could be developed for syntheses of preparative value.

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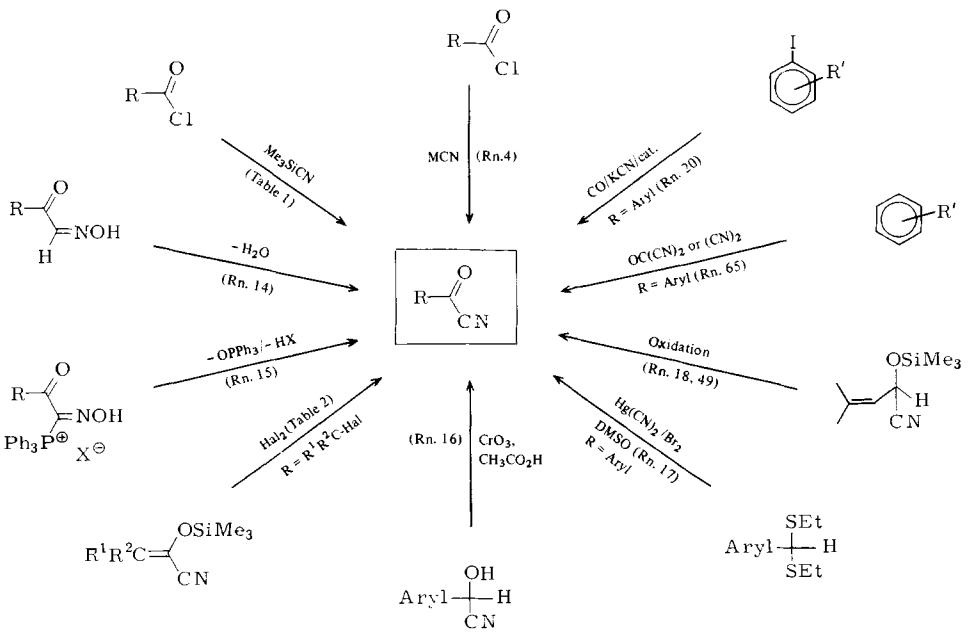
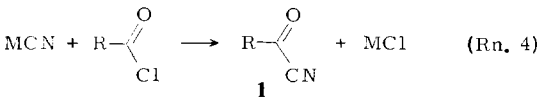
3. Synthesis of Acyl Cyanides



Scheme 1.

The most important synthetic routes to acyl cyanides **1** are shown in Scheme 1.

3.1. Acyl Cyanides from Carboxylic Acid Halides



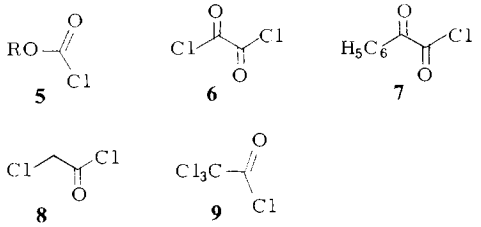
MCN + R–C(=O)–Cl ⟶ R–C(=O)–CN + MCl (Rn. 4)

1

Rn.	MCN	Conditions	R	Yield [%]
4a	CuCN	Acetonitrile, 80°C, 15 min	Aryl, alkyl	50-75 [5]
4b	CuCN	LiI, ether, 30°C, 2h	C_6H_5	62 [6]
4c	TlCN	Ether, ethyl acetate 20°C, 1-3 h	Aryl	45-89 [4]
4d	NaCN (CuCN)	Org. solvent 50 to 300°C	Aryl, alkyl	50-95 [17]
4e	KCN	[18]Crown-6, CH_2Cl_2-H_2O	RO	62-94 [7]
4f	Et_4NCN	CH_2Cl_2, −40 to +20°C	R_2N, C_6H_5O	≈90 [8]
4g	NaCN	TBABr [a], CH_2Cl_2-H_2O	Aryl	50-75 [9]
4h	Me_3SiCN	Cf. Tables 1 and 2	RO, (Aryl?) Alkyl	50-100 [10, 11]
4i	nBu_3SnCN	Without solvent, 75°C, 5 min	Aryl	80-95 [12]

[a] TBABr = tetra-*n*-butylammonium bromide.

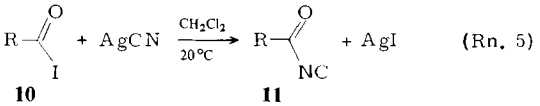
The classical reaction of carboxylic acid halides with heavy metal cyanides (Cu^I, Hg^I, Ag^I, low cyanide concentration!) demands heating for hours at 120—160°C and for aliphatic derivatives the use of acid bromides[1]. In the latter case the addition of phosphorus pentoxide increases the yield[5]. CuCN, complexed with acetonitrile as solvent yields acyl cyanides in 50—75% yield (Rn. 4a) already after 15 minutes at 80°C—even from aliphatic acid chlorides. This method does not succeed with the acid chlorides **5** (too unreactive) and **6** (exothermic reaction). Compound **7** reacts—probably *via* radical decarbonylation[13]—to give benzoyl cyanide. From **8** and **9** only products of cyanation are obtained[6].



5 **6** **7** **8** **9**

The activation of copper cyanide by lithium iodide is noteworthy, but is not suitable for the synthesis of aliphatic acyl cyanides[6] (Rn. 4b). Thallium(I) cyanide reacts particularly smoothly with aromatic acid chlorides, even if they are activated by electron acceptors[4] (Rn. 4c). However, it is questionable whether the high yield of 85% of *p*-nitrobenzoyl cyanide (Rn. 4a 64%) justifies preparation of the reagent from anhydrous thallium(I) phenolate and hydrocyanic acid. After all, this cyanide is sufficiently reactive to convert even **5** into cyanoformic ester in 90% yield, while aliphatic acid chlorides furnish mostly only dimeric acyl cyanides **3**[4].

In contrast to the well known alkyl isocyanides, the formation of acyl isocyanides **11** from heavy metal cyanides could only recently be demonstrated[14] through the use of acyl *iodides* **10**. Compounds **11** easily rearrange into acyl cyanides (especially by catalysis of 4-pyrrolidinopyridine[15]), for which reason they were presumably overlooked.

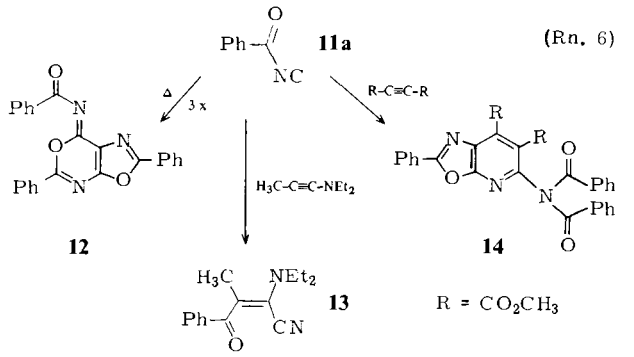


R–C(=O)–I + AgCN $\xrightarrow[20°C]{CH_2Cl_2}$ R–C(=O)–NC + AgI (Rn. 5)

10 **11**

R = Aryl, Alkyl

When heated above its melting point, the isolable benzoyl isocyanide **11a** trimerizes to a compound which *Nef*[16] had already obtained as a "trimeric benzoyl cyanide" and whose hitherto accepted structure[1] was rejected[14] in favor of **12**. The reaction **11a**→**13** proves the acylation potential of **11a**, while its reaction to give **14** demonstrates its ability to undergo cycloadditions.

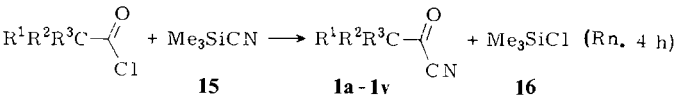


High yields of **1** are also obtained from the heterogeneous reaction of sodium (potassium) cyanide with acyl chlorides[17a] or anhydrides[17b], especially in the presence of Cu^{I} salts[17c] (Rn. 4d). From an industrial point of view syntheses of **1** from anhydrous hydrocyanic acid have been developed[17c]. By means of solid-liquid phase-transfer catalysis the unreactive chloroformic acid esters **5** react smoothly with potassium cyanide to yield cyanoformic esters (Rn. 4e)[7]. Tetraethylammonium cyanide, which is used for a general nitrile synthesis[8a], does not require a phase-transfer catalyst because of its high solubility in dichloromethane. Due to its high reactivity, however, chloroformic alkyl esters will be decarboxylated, so that only chloroformic aryl esters and -dialkylamides are suitable educts (Rn. 4f)[8a]. While the formation of dimers according to Rn. 4e and 4f does not occur, it cannot be avoided in the solid-liquid phase-transfer catalyzed reaction between aromatic acid chlorides and sodium cyanide (Rn. 4g) because of the high cyanide ion concentration (cf. Rn. 2). With strongly electron accepting substituents dimerization becomes the main reaction[9] (cf. Rn. 67). Without phase-transfer catalyst, however, on addition of hydrocyanic acid and a tertiary amine, the reaction stops at **1** (≈90%) in the case of benzoyl chloride[9b].

(For the Friedel-Crafts synthesis of aromatic acyl cyanides cf. Section 4.4.2, Rn. 65.)

A general synthesis, according to which the preparatively more important aliphatic acyl cyanides are readily accessible in high yield, was recently achieved independently by two groups[10, 11] using cyano(trimethyl)silane **15**[18] (Rn. 4h). This reagent, which adds in high yield to various carbonyl groups[18a, d, 19, 20] was already known to react smoothly with chloroformic ester (70%)[18d]. Table 1 contains the aliphatic and benzylic acyl cyanides **1a**—**1v** which are formed in a reaction of equimolar components in the absence of solvent. The autocatalyzed reaction[10] is easily monitored by IR spectroscopy and is strongly accelerated by bromo(trimethyl)silane[10], zinc iodide[11] or aluminum chloride[11].

Table 1: Synthesis of aliphatic α,β-unsaturated acyl cyanides (**1a-1v**). *Experimental Procedure* [11]: Under the reaction conditions given in Table 1 equimolar quantities of carboxylic acid chloride and **15** are stirred without solvent and with exclusion of moisture (if necessary addition of ≈0.5% ZnI_2). The course of the reaction is followed by IR-spectroscopy by means of the nitrile bands. After **15** is completely consumed the solution is distilled or allowed to react directly.

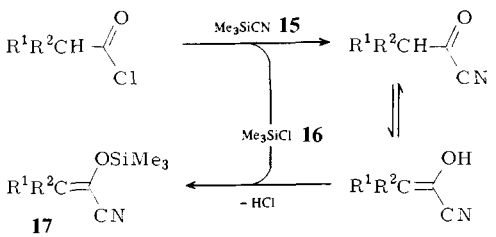


15 **1a-1v** **16**

No.	R^1, R^2, R^3	*t* [h]/*T* [°C]	Yield [%]	Yield [%] Other methods
1a	H, H, H	24/25 [a]	100 [b] [11b]	[1]
1b	CH_3, H, H	1.5/80 [a]	94 [11a]	60 [6, 21]
		2/60	40 [10]	
1c	C_2H_5, H, H	2/100 [a]	92 [11a]	51 [6]
		2.5/70	33 [10]	
1d	$-(CH_2)_2-$, H	5/100 [a]	100 [b] [11d]	—
1e	$CH_3-CH=$, H	2.5/100	90 [11a]	50 [6, 22]
1f	$CH_3=CH-CH_2$, H, H	36/20	100 [b] [11b]	—
1g	C_6H_5, C_6H_5, H	192/20	100 [b] [11b]	—
1h	$C_6H_5-CH(CH_3)$, H, H	2.5/120	100 [b] [11b]	—
1i	CH_3O-CH_2, H, H	72/25	80 [b] [11b]	—
1j	CH_3, CH_3, H	0.5/100 [a]	92 [11a]	59 [21]
1k	C_2H_5, CH_3, H	7/100 [a]	100 [b] [11d]	—
1l	$C_6H_5CH_2$, CH_3, H	0.5/100 [a]	100 [b] [11d]	—
1m	$-(CH_2)_5-$, H	1/100 [a]	100 [b] [11d]	—
1n	CH_3, CH_3, CH_3	3/100 [a]	91 [11a]	87 [6]
		2.5/70	65 [10]	
1o	CH_3, Cl, H	1/50	90 [11a]	—
		2.5/60	52 [10]	
1p	CH_3, Br, H	1.5/70	81 [10]	—
1q	CH_3, I, H	5/20	100 [b] [11b]	—
1r	Cl, H, H	3/65	53 [10]	—
1s	Br, C_2H_5, H	1.5/65	64 [10]	—
1t	Br, *i*-C_3H_7, H	120/20	100 [b, c] [11b]	—
1u	Br, Br, H	4/60	69 [10]	—
1v	$Cl_2C=CCl-CCl=$, Cl	72/25	46 [23]	—

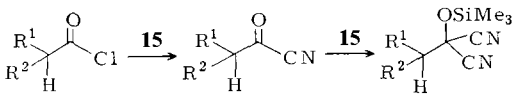
[a] Addition of catalytic amounts of Lewis acid. [b] Conversion and purity determined by IR-spectroscopy. [c] Secondary reaction to give a 2-(trimethylsiloxy)-2-propenonitrile derivative (Rn. 7).

Even α-halogenated acyl cyanides are accessible by this convenient route (cf. also Table 2). In some cases with acyl cyanides carrying α-hydrogen a consecutive reaction is observed, particularly on addition of a catalyst, yielding 2-(trimethylsiloxy)-2-propenonitriles **17**. The formation of **17** is probably due to the ready enolization of these acyl cyanides which are then *O*-silylated to **17** by the generated chloro(trimethyl)silane **16**. Accordingly, only **17** ($R^1 = C_6H_5$, $R^2 = H$) is isolated from phenylacetyl chloride instead of the acyl cyanide. This reaction can be extended into a general synthesis[11c] of **17** by addition of triethylamine.



A further difficulty arises with acyl cyanides which add another molecule of **15** to the carbonyl group. With the less enolizable acyl cyanides of type **18** (*e.g.* **1d** or **1j**, cf.

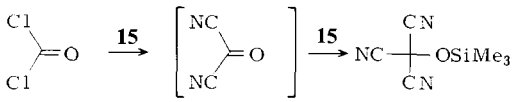
Table 1) adducts **19** are formed in a slower subsequent reaction[11b]. When exactly one equivalent of **15** is used with ZnI_2 catalysis this undesirable consecutive reaction can be completely suppressed[11d]. If under these conditions ZnI_2 is replaced by $(n\text{-}C_4H_9)_4N^{\oplus}I^{\ominus}$, compound **19** ($R^1$, $R^2 = CH_3$, 50%) is exclusively formed although acid chloride (50%) is still present. Thus, in this case the second step of the reaction proceeds much faster than the first[11d].



(Rn. 8)

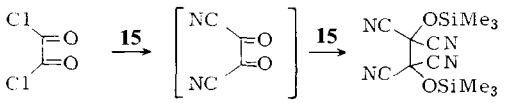
18 **19**

Even without catalysis this mode of reaction can be observed, if as in the examples **20, 22,** and **24** the intermediate acyl cyanides possess a high carbonyl activity, so that the adducts **21, 23** and **25** are formed immediately[18a].



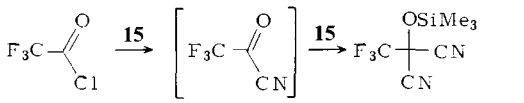
(Rn. 9)

20 **21**



(Rn. 10)

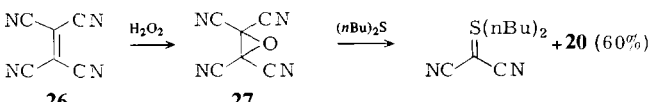
22 **23**



(Rn. 11)

24 **25**

Carbonyl cyanide **20** is, however, accessible by pyrolysis of acetylated bis(isonitroso)acetone, whereby the yield has been improved from 25%[1] to 40%[24]. The route *via* tetracyanoethylene **26** and its oxide **27**[25] appears even more practical, the latter furnishing[26] 60% of **20** on reaction with dibutyl sulfide (Rn. 12).



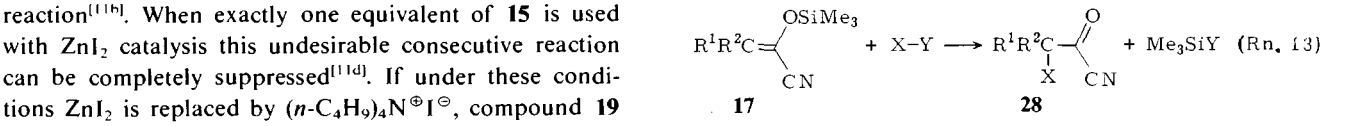
(Rn. 12)

26 **27**

Cyano(trimethyl)silane **15** should also smoothly convert aromatic acid chlorides into acyl cyanides—a reaction for which tri-*n*-butyl(cyano)tin was recently described as particularly suitable (Rn. 4i). With aliphatic acyl chlorides whose alkyl groups are primary or secondary this reagent furnishes only dimeric acyl cyanides[12].

The above preparation of the 2-(trimethylsiloxy)-2-propenonitrile derivative **17** can be utilized for a very efficient synthesis of α-halogenoacyl cyanides **28**. Reaction of **17** with halogens proceeds fast and practically quantitatively[11a]; therefore, the sensitive acyl cyanides **28** (Table 2) need not be distilled for further reactions.

Tabelle 2. α-Haloacyl cyanides **28** *via* desilylating halogenation of **17** [11].



(Rn. 13)

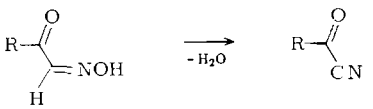
17 **28**

R^1	R^2	X	Y	*t* [min]/ *T* [°C]	Yield [%] after [11]	Yield [%] after other methods
H	H	Cl	Cl	10/0	100 [a]	53 [10]
H	H	Br	Br	10/20	100 [a]	66 [10]
H	H	I	Cl	240/0	100 [a]	—
CH_3	H	Cl	Cl	10/0	96	52 [10]
Cl	H	Cl	Cl	10/0	100 [a]	[27]
Cl	*Cl*	*Cl*	Cl	10/0	95	80 [28]

[a] Acyl cyanide was not isolated, conversion and purity determined by IR-spectroscopy.

3.2. Acyl Cyanides from Aldehydic and Ketonic Derivatives

The dehydration of aldoximes with acetyl chloride, thionyl chloride, and similar reagents to give nitriles has also been applied[1,24a] to α-oxo-aldoximes **29.** Instead of **29** the corresponding derivatives from α-oxo-aldehydes and 1-amino-4,6-diphenyl-2-pyridone are suitable for the formation of aromatic acyl cyanides by thermolysis in 85–95% yield[24b].

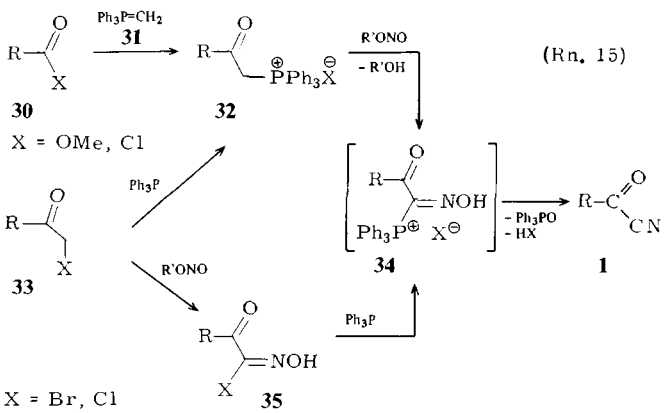


(Rn. 14)

29 **1**

R = Aryl, Alkyl (40-75%) [1]

The spontaneous decomposition of the intermediary oximes **34** into the acyl cyanides **1** represents a related reaction. Compound **34** is formed by nitrosation of **32**[22,29] as well as by the reaction of **35** with triphenylphosphane[30]. The phosphonium salts **32** are accessible from the carbonic acid derivatives **30** and the Wittig reagent **31**[31], or from halomethyl ketones **33** and triphenylphosphane[32];

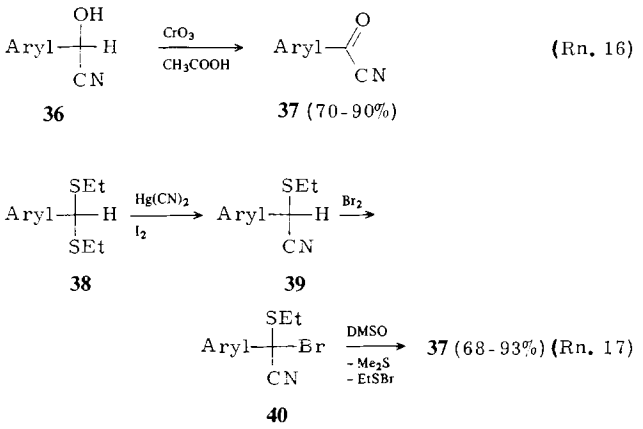


(Rn. 15)

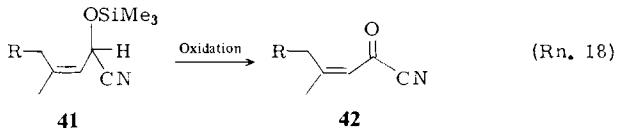
30 **32** **33** **34** **1** **35**

the oximes **35** are obtained from **33** by nitrosation[30]. The alcohol which is generated by nitrosation of **32** instantaneously converts the aliphatic acyl cyanides produced into esters (cf. Section 4.4.1).

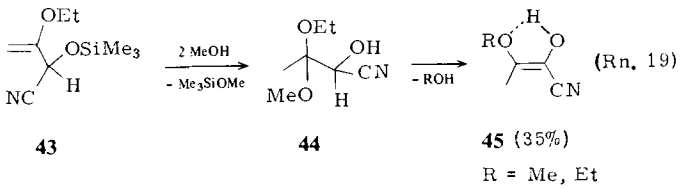
The known oxidation of aromatic cyanohydrins **36** with chromic acid/glacial acetic acid has been varied in several ways[1]. Thus, the aromatic acyl cyanides **37** are produced in a type of Kornblum-oxidation[33] from the unstable α-bromo-α-(ethylthio) derivatives **40** which in turn are formed[34] *via* **38** and **39** (DMSO = dimethyl sulfoxide).



Supposedly, the oxidation of the adducts of cyanotrimethylsilane to α,β-unsaturated aldehydes **41**[35] is, much more important. Although **42** may be isolated, its significance depends on the subsequent products (see Rn. 18 and 49)[36].

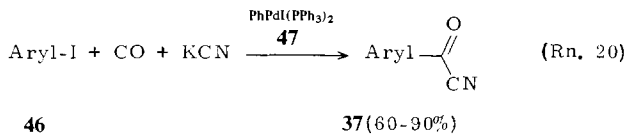


The methanolysis of the cyano(trimethyl)silane adduct **43** according to Rn. 19 can be construed as an intramolecular disproportionation in which the α-alkoxyacyl cyanides formed *via* **44** can be described as enols **45**[37a].



3.3. Acyl Cyanides Through Cyanocarbonylation

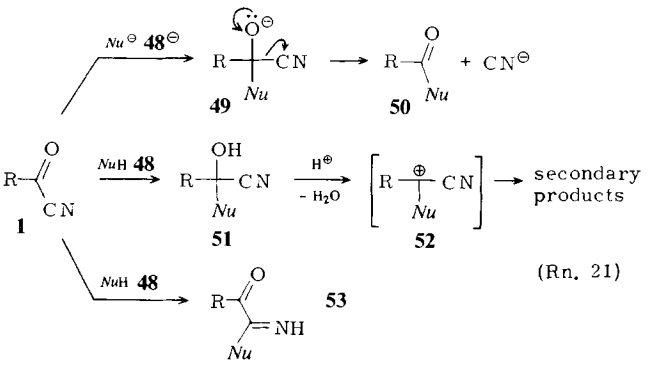
A novel approach to aromatic acyl cyanides has been opened up by the cyanocarbonylation of aryl iodides **46** by means of the palladium complex **47**[37b].



4. Reactions of Acyl Cyanides

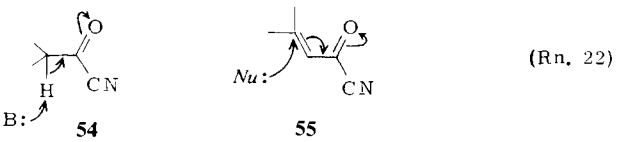
4.1. General Rules

The electrophilicity of both functions in acyl cyanides is enhanced by the proximity of the CO and CN groups (see Rn. 21). As a rule, nucleophiles **48** preferentially attack the CO group. The cyano group as a pseudohalogen is thereby displaced with formation of **50** if its nucleophilic fugacity is increased by protic solvents and the anionic intermediate **49** is present in sufficient concentration.



The cyanide **1** acts as a mild acylating agent (Section 4.4) leading to CC fission with water (Rn. 1!), alcohols, amines, CH-acidic compounds *etc.* Under aprotic conditions or in strongly acid media the lifetime of the adduct **51** is apparently sufficient to produce without C—C fission, via **52**, the typical reaction products of carbonyl compounds with nucleophiles which result from loss of water (section 4.2).

Finally, one must bear in mind the effect of the CO group in **1** on the neighboring C-skeleton: deprotonation as in **54** or Michael-additions as in **55** may occur (*cf.* Sections 4.2.3 and 4.2.4).



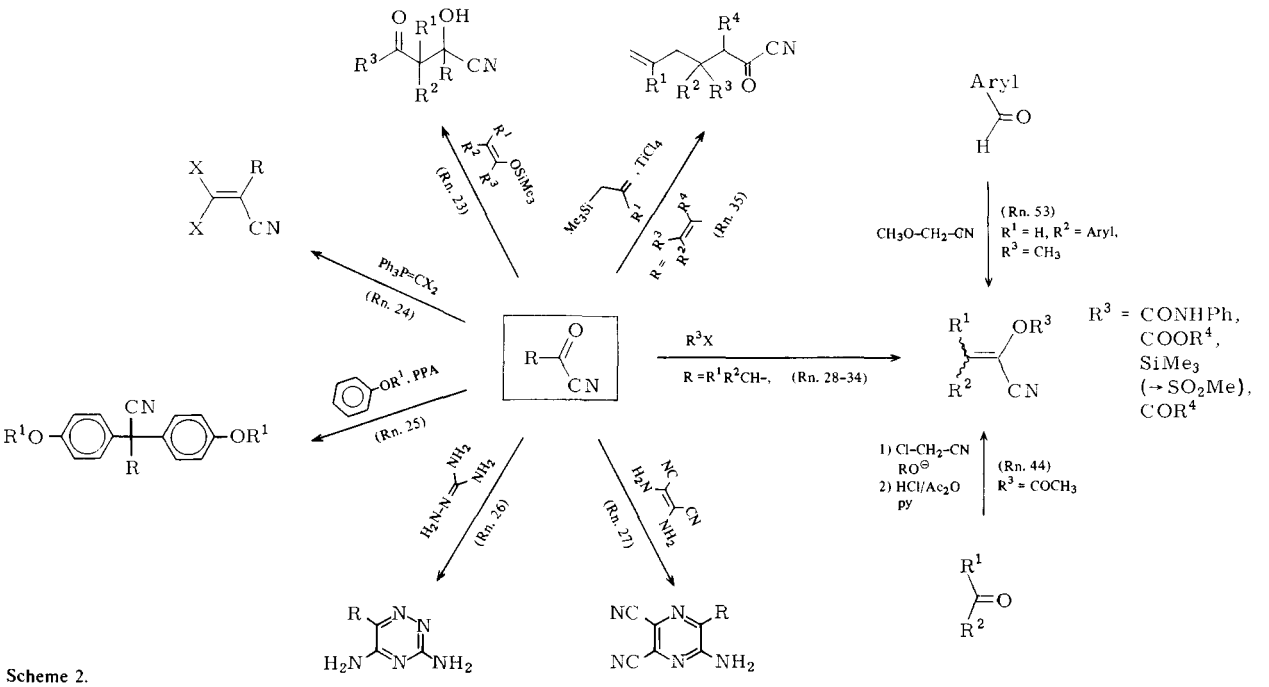
Additions to the CN-group to give **53**, *i.e.* with preservation of the CO-function, are only achieved with soft nucleophiles (H_2S) or under strongly acidic conditions which substantially increase (*cf.* Eq. 44) the electrophilicity of the nitrile group through protonation (*cf.* reactions of nitrilium salts). This is exemplified by the saponification of **1** to α-oxoamides or α-oxoacids[1].

4.2. Reactions of the CO-Group with Preservation of the C-Skeleton

Typical reactions of the CO-group **1** with preservation of the carbon skeleton are collected in Scheme 2.

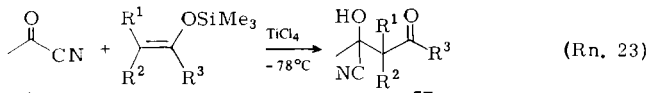
4.2.1. Reactions of the CO-Group with C-Nucleophiles

Reactions of **1** with anionic C-nucleophiles terminate with cleavage of cyanide (for older reactions, see[1]); in contrast, as already mentioned, this does not take place in the smooth addition of cyanotrimethylsilane to activated acyl cyanides (Rn. 8—11). While acyl cyanides cause C-acylation of enolate ions (Rn. 60, 61), the reaction of silyl enol ethers **56** in presence of $TiCl_4$ terminates at the stage of the aldol adducts **57**. Allyltrimethylsilane is added simi-



Scheme 2.

larly[39] (*cf.* also the 1,4-addition to α,β-unsaturated acyl cyanides; Rn. 35).

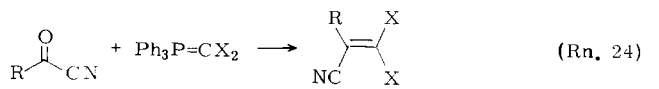


(Rn. 23)

1a **56** **57**

R^1, R^2 = H, Alkyl
R^3 = H (≈35%)
R^3 = Alkyl, Aryl (67-93%)

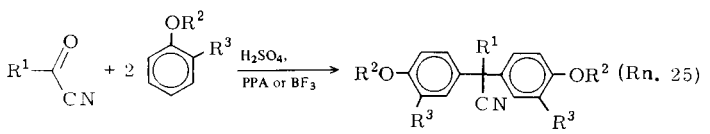
Smooth Wittig reactions take place with the dihalomethylenephosphorus ylides **58**[40].



(Rn. 24)

1 **58**, X = Cl, Br **59**, R = C_6H_5, X = Cl (75%)
60, R = Cl_2C=CH, X = Br (77%)

The condensation with phenols in strong acid[41], which so far has only been possible for aromatic acyl cyanides, has been extended to acetyl cyanide and carbonyl cyanide (reaction with dimethylaniline is known[1]) and even applied to phenolic ethers **61** resulting in bisphenol derivatives **62**[42] (PPA = polyphosphoric acid) (cf. also the synthesis of aromatic acyl cyanides from carbonyl cyanide, Section 4.4.2, Rn. 65).

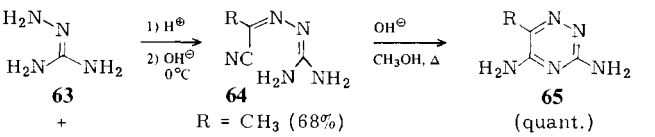


(Rn. 25)

61 **62**

4.2.2. Reactions of the CO Group with N-Nucleophiles

The condensation of acyl cyanides with phenylhydrazine or thiosemicarbazide in strongly acid medium with elimination of water[1] can also be extended to aminoguanidine **63**[43,44]. On warming with methanolic sodium hydroxide, the products **64** quantitatively undergo ring-closure to yield **65**[44].



63 + **64** **65**

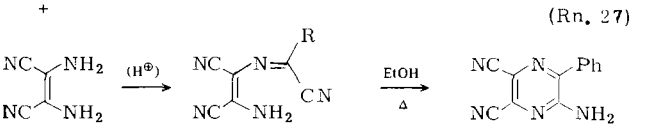
R = CH_3 (68%)
R = Aryl (≈70%)
(quant.)

(Rn. 26)

1, R = Alkyl, Aryl

+

(Rn. 27)



66 **67** **68**

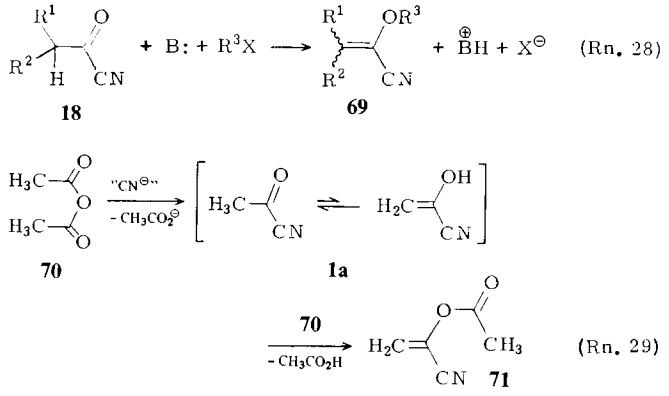
(40-75%)
R = Ph (quant.)

The dinitrile of diaminomaleic acid **66** converts **1**, even with catalytic amounts of acid, into the Schiff's bases **67**, which can be cyclized to pyrazines **68**[45].

4.2.3. Preparation of Enol Derivatives

Since acyl cyanides of type **18** can, in principle, be deprotonated, enol derivatives **69** should be accessible according to Rn. 28. Thus, for instance, the enol ester **71**[46] and not acetyl cyanide **1a** is formed by interaction of acetic anhydride **70** and potassium cyanide in the presence of [18]crown-6.

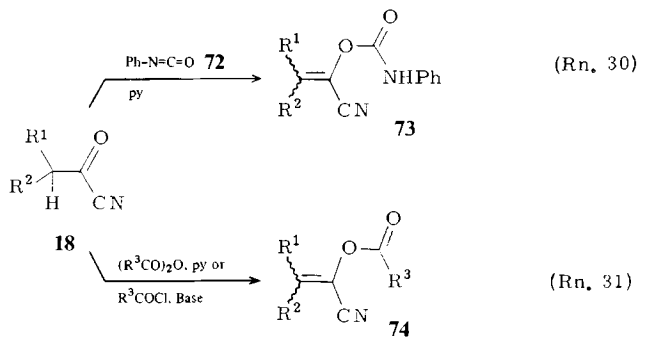
The fact that excess of acetic anhydride acylates the enolic form of the intermediate acyl cyanide **1a** can be demonstrated by using mixed anhydrides, as well as by acylation of **18** with phenyl isocyanate **(72)** yielding **73**[46].



(Rn. 28)

(Rn. 29)

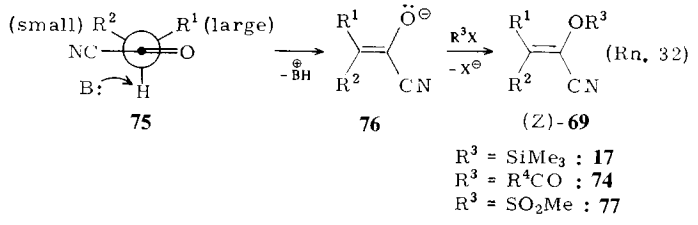
Compound **74** is produced even more conveniently by acylation with acid chlorides or anhydrides in the presence of pyridine or [2,2,2]-diazobicyclooctane (yield 35–75%)[46]. The rate of this acylation depends on the concentration of acyl cyanide and base, but scarcely, if at all, on that of the acid chloride. Thus the deprotonation of **18** may represent the rate determining step[46].



(Rn. 30)

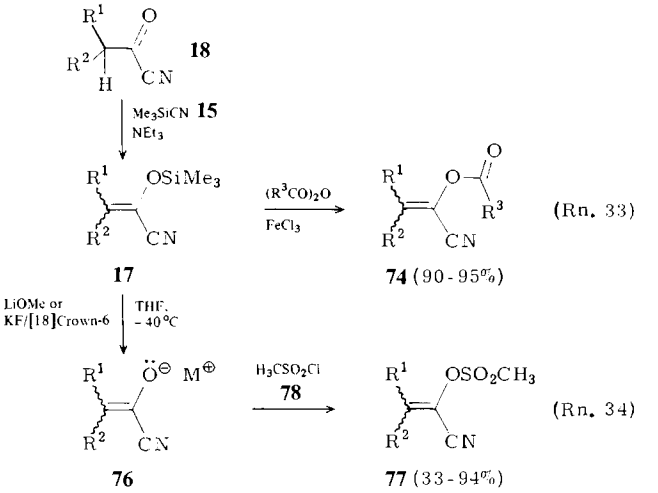
(Rn. 31)

In order to gain maximum π-conjugation the transition state should develop mainly from the conformation **75**. Here, the large group R^1 is located *syn* to the oxygen atom, which in comparison to the CN group is substantially smaller. Thus, according to Rn. 32 the products **(17, 74, 77)** should be produced in their *Z*-form *via* the *Z*-form of the enolate **76.** In fact **74** ($R^1=CH_3$, $R^2=H$, $R^3=COC_2H_5$) is present as a *Z/E* mixture (80/20)[47]. A corresponding situation applies to **17** for the same reasons. For instance, the derivatives $R^2=H$, R^1=t-butyl, phenyl, Br, I contain the large substituents R^1 and $(CH_3)_3SiO$ exclusively in the *cis*-arrangement (*Z*-form)[11c]. Whether formation of (*Z*)-**69** profits additionally from the energetically favorable *trans*-arrangement[48] of R^1 as σ_R-donor[49] with the cyano-group as acceptor is still unclear.



(Rn. 32)

The previously mentioned silylation of **18** to **17** belongs here[11c]. By analogy to silyl ethers[50], **17** is easily transformed with acid anhydrides and $FeCl_3$ catalysis into the enol esters **74**[11c]. But above all, **17** makes it possible for the first time to prepare the configurationally stable enolates **76** by desilylation with lithium methoxide, or better with potassium fluoride/[18]crown-6 [11c]. The most important reaction of **76** with electrophiles so far is the successfully tested[11c] mesylation with **78** to give the esters **77**, whose synthetic potential exceeds to some extent the frequently used α-chloroacrylonitrile[11b] (THF = tetrahydrofuran).



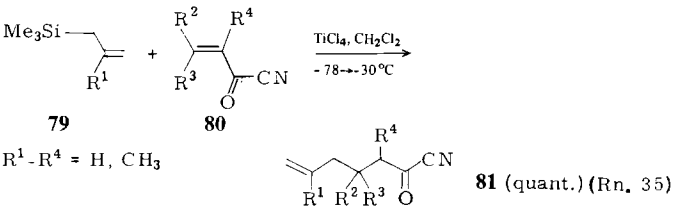
(Rn. 33)

(Rn. 34)

As members of synthetic sequences, importance also attaches to the acyl cyanide-enol derivatives **102** and **115,** in which the C=C bond is the newly formed one (Rn. 44 and 53).

4.2.4. Michael-Additions to α,β-Unsaturated Acyl Cyanides

As recently shown, the $TiCl_4$-catalyzed reaction of allyl silanes **79** with α,β-enones[51] may be extended to α,β-unsaturated acyl cyanides **80,** which react under milder conditions apparently quantitatively[52] (Rn. 35). By rapid work-up, the acyl cyanides **81** can be isolated if carbonic acids (+H_2O) or their methyl esters (+CH_3OH) are not wanted.

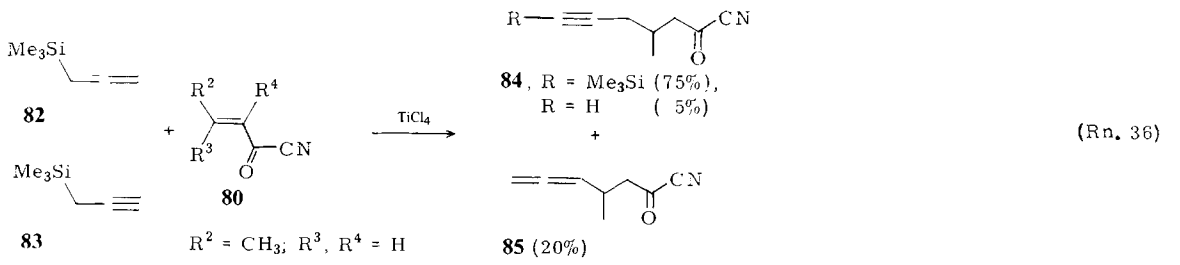


(Rn. 35)

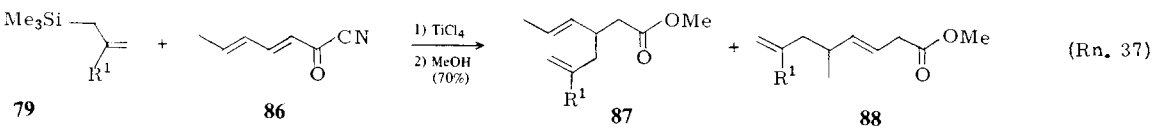
The propadienylsilane **82** behaves, correspondingly, in the same fashion. It contains 20% **83** and furnishes the mixture **84/85.**

Compound **79** adds to **86** in the β- as well as in the δ-position to give a mixture of **87** and **88** (*ca.* 1:1).

Because α,β-unsaturated esters do not react with allyl silanes, and since in the corresponding acid chlorides the halogen is substituted, the reactions according to Rn. 35–37 may acquire greater preparative importance.



(Rn. 36)



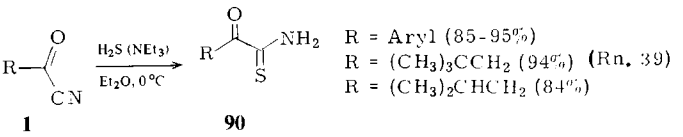
(Rn. 37)

4.3. Reactions of the CN-Group with Preservation of the C-Skeleton

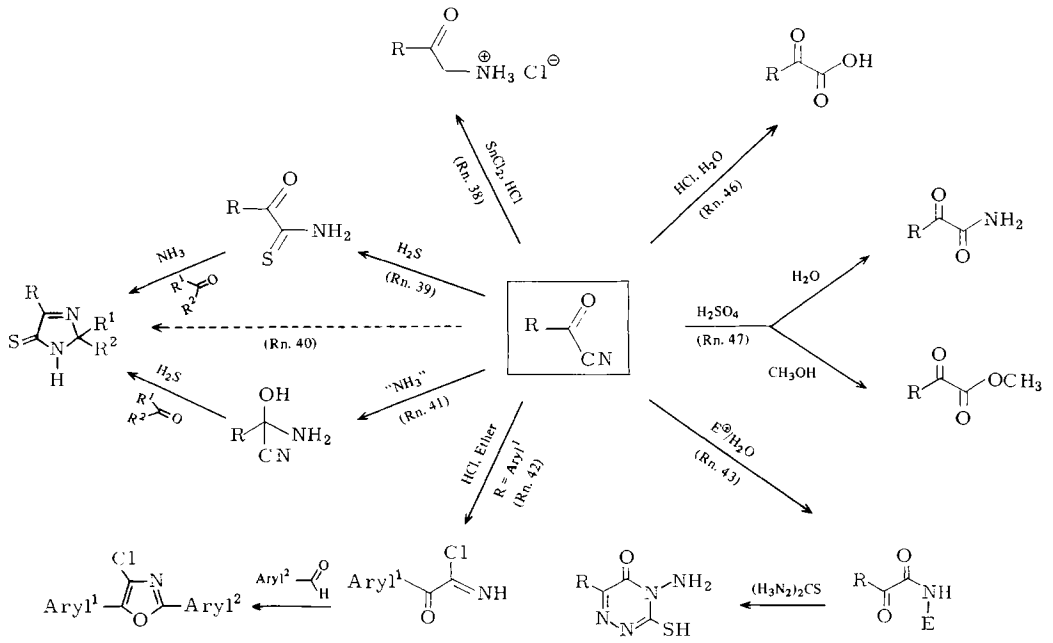
Scheme 3 shows typical reactions of the CN-group in **1** with preservation of the carbon skeleton.

While aromatic acyl cyanides **1** (R = Ar) are reduced by excess of lithium aluminum hydride or hydrogen/palladium in glacial acetic acid to give the pharmacologically interesting 2-amino-1-aryl-ethanols[1], Stephens' reagent

The known base-catalyzed addition of H_2S to nitriles resulting in thioamides cannot only be accomplished[1] with deactivated acyl cyanides **1** (R = RO, RNH, R_2N), but α-oxothioamides **90**[5,55] are generally produced under mild conditions.



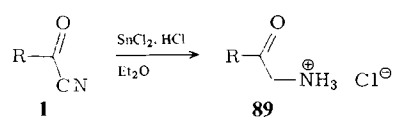
(Rn. 39)



Scheme 3.

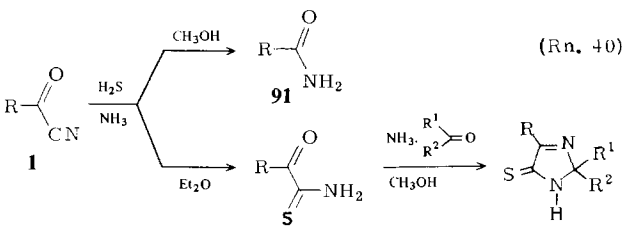
$SnCl_2$/HCl/ether attacks only the nitrile group. The sensitive aminoketones **89** are formed relatively smoothly[53a] (see, however, reduction with $TiCl_3$[53b]).

A selective, catalyzed hydrogenation is reported also to be possible[54].

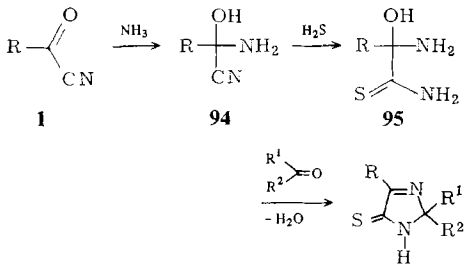


(Rn. 38)

Reaction 40 demonstrates how decisively the solvent influences the course of the reaction: While the mixture



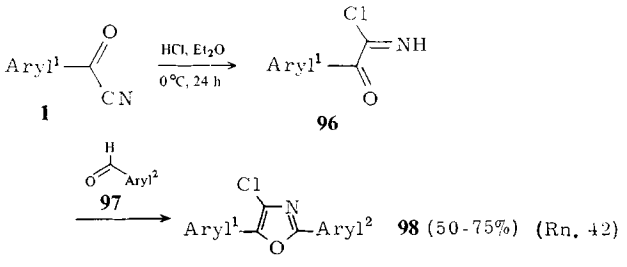
(Rn. 40)



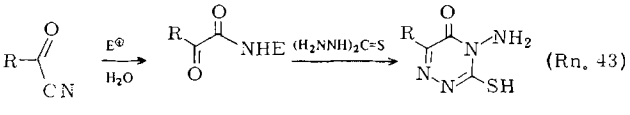
1 **94** **95** **93** (Rn. 41)

H_2S/NH_3 with benzoyl cyanide in methanol reacts with acylating cleavage to give benzamide, H_2S adds in ether to the nitrile group forming thioamide **92,** in spite of the presence of the same base[56]. In methanol, **92** reacts with ammonia and aldehydes or ketones very rapidly and almost quantitatively to give 3-imidazoline-5-thiones **93**[5]. Compound **93** is also formed stepwise from acyl cyanides *via* the semiaminal **94**[57].

The fact that the nitrile group in aromatic acyl cyanides can be converted into the imidochlorides **96** has already been known for the Houben-Hoesch reaction of phenols to give α-diketones[1]. The cyclization of **96** with aromatic aldehydes **97** to give the oxazoles **98** has now also been successfully carried out[58].



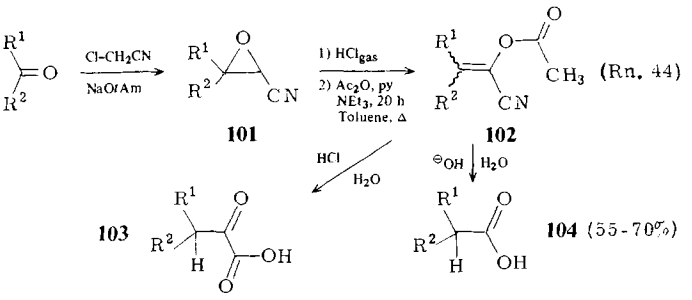
1 **96** **97** **98** (50-75%) (Rn. 42)



E = H: **99a** **100**
E = R'_3C: **99b**

Aliphatic acyl cyanides are also transformed by gaseous hydrogen chloride into imide chlorides, which are smoothly hydrolyzed to the ketoamides **99a**[59] (see Rn. 47). In a similar fashion with tertiary alcohols and the corresponding alkenes[60a] or ethers[60b] in the presence of acid the alkylated ketoamides **99b** are obtained in a Ritter reaction. Both derivatives serve as important building blocks for heterocycles, *e.g.* for triazinones **100** (herbicides)[59b,60b,60c].

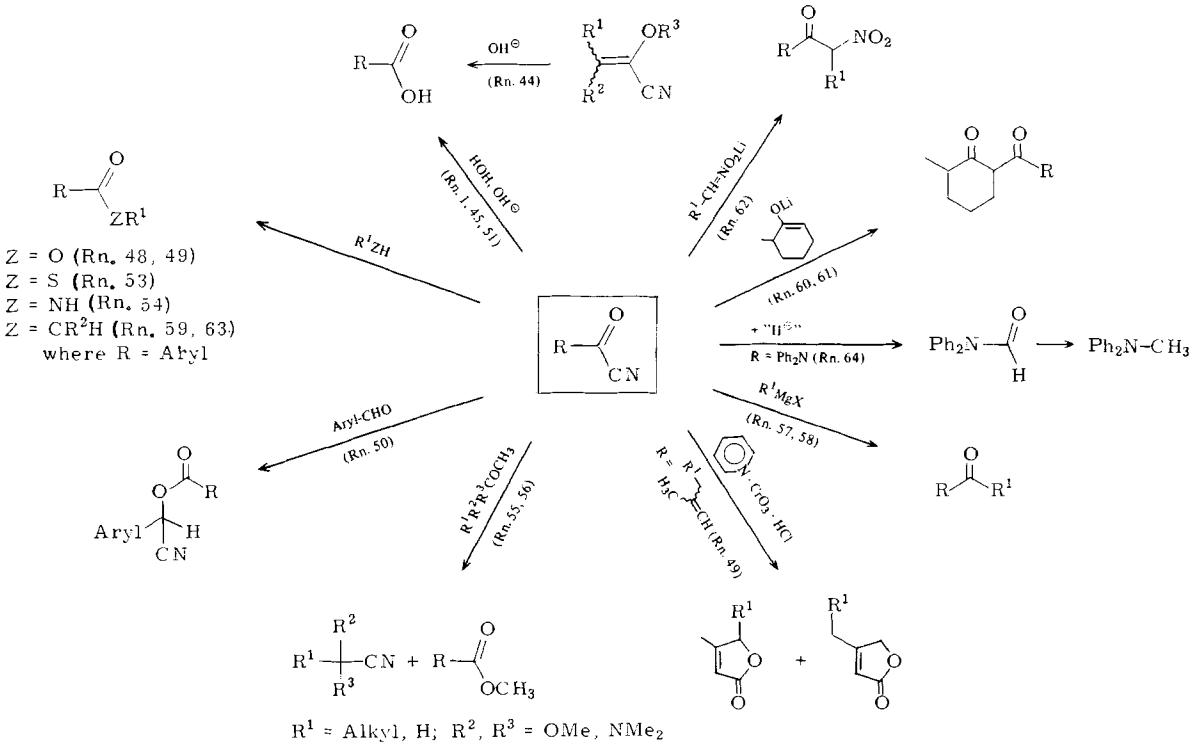
Acyl cyanides appear as intermediates in a synthetic sequence in which ketones are converted into homologous α-ketocarboxylic acids **103** or, with loss of the cyano-group, into carboxylic acids **104.** The intermediates **101** and **102**[61] are isolable (Rn. 44).



101 **102** **103** **104** (55-70%)

4.4. Reaction of the CO-Group with Separation of Cyanide Ions

As already shown, in reaction 21, acyl cyanides act in this important cleavage reaction as mild acylating agents



Z = O (Rn. 48, 49)
Z = S (Rn. 53)
Z = NH (Rn. 54)
Z = CR^2H (Rn. 59, 63)
where R = Aryl

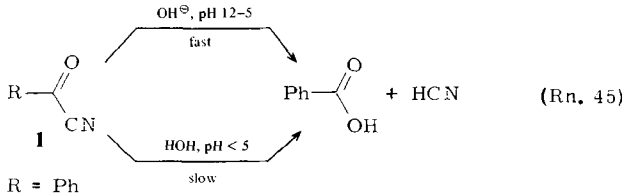
R^1 = Alkyl, H; R^2, R^3 = OMe, NMe_2

Scheme 4.

for hetero- and C-nucleophiles (see Scheme 4). Compared with acid chlorides their advantage rests on the low acidity of the hydrocyanic acid formed. Therefore, no auxiliary base is needed, even with amines as nucleophiles. Similarly favorable properties are shown only by the *N*-acylimidazoles[62].

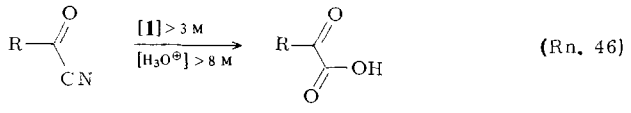
4.4.1. Reactions with HOH, ROH, RNH_2, and RSH

The reaction of benzoyl cyanide (**1**, R = Ph) with *water*, resulting in the displacement of the cyano-group, shows a pronounced pH-dependence. In the region of pH 12–5 a fast bimolecular reaction with hydroxyl ions takes place. At lower pH values water attacks appreciably slower, whereby this cleavage is subject to a general base catalysis, so that acids inhibit the cleavage of acyl cyanide (Rn. 45: important observation for the work-up of reaction mixtures, *e.g.* according to reaction 38, and also for the electrophilic substition of aromatics by acyl cyanides as in Rn. 25 and 65!)



(Rn. 45)

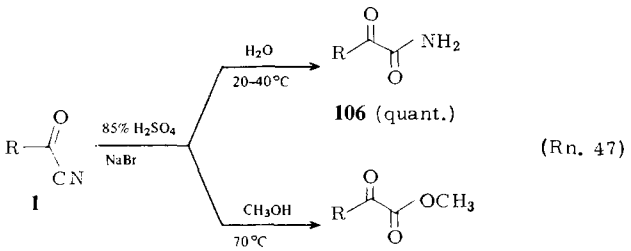
1 R = Ph



(Rn. 46)

1 R = CH_3, C_2H_5 **105**

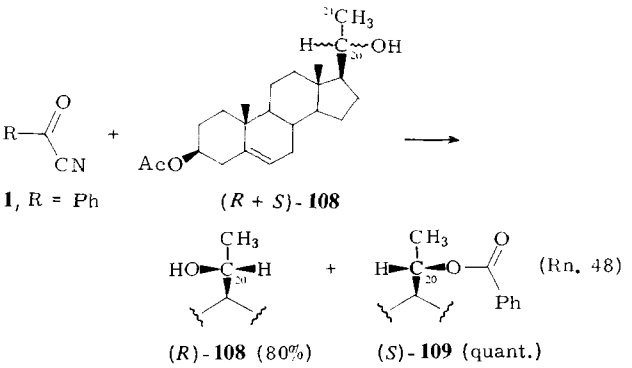
With aliphatic acyl cyanides the hydrolytic fission slows down with increasing concentration of strong acid (up to *ca.* 8 M). Only then does acid-catalysis start, which, however, now leads to the α-oxoacid **105** as in reaction 46, if at the same time the concentraion of **1** is >3 M[63]. Saponification of the nitrile group is strongly catalyzed by bromide ions. Thus, the addition of sodium bromide to benzoyl cyanide in 85% sulfuric acid causes a strongly exothermic reaction. After addition of water, benzoyl formamide **106** can be quantitatively isolated, while with methanol 85% methyl benzoylformate **107** is formed[64].



(Rn. 47)

1 R = Ph **106** (quant.) **107** (85%)

The well known fission of **1** by *alcohols* has proved to be a highly selective reaction for derivatizing hydroxysteroids in presence of benzoyl cyanide (**1**, R = Ph). By this procedure, epimers are separable because of their different rates of benzoylation. As demonstrated by reaction 48, this separation is even successful if the hydroxyl group is not bound to the rigid steroid framework, as in the case of the



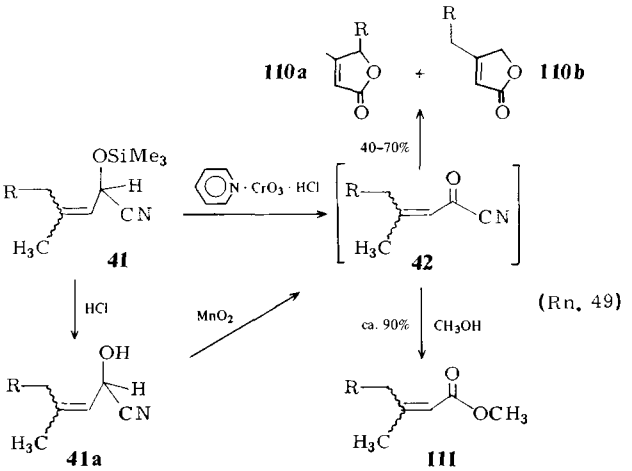
1, R = Ph (*R* + *S*)-**108**

(Rn. 48)

(*R*)-**108** (80%) (*S*)-**109** (quant.)

mixture of (20*R*)- and (20*S*)-3β-acetoxy-20-hydroxy-5-pregnene (*R*+*S*)-**108**, from which only the *S*-form is benzoylated to (*S*)-**109**. The reactivity of **1**, R = Ph, towards hydroxy-steroids follows the sequence: 21 > 17β > 3β > 6α,3α ≫ 20α > 20β ≫ 7β ≫ 7α > 6β > 2β > 22α[65a].

The smooth formation of esters from acyl cyanides is particularly advantageous for the conversion of sensitive, unsaturated aldehydes into carboxylic acid methyl esters **111**. The appropriate cyanohydrins **41a** or their trimethyl silylethers **41** (+ $H^{\oplus}$) are dehydrated with active manganese dioxide in methanol (yields ≈90%[36a]). On the other hand, the importance of the oxidation of the allyl ethers **41** with pyridinium chlorochromate in absence of alcohol lies in the unusual oxidative intramolecular acylation to butenolides (*e.g.* **110a** and **110b**)[36b].

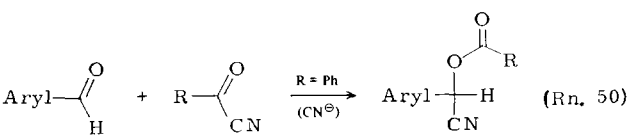


(Rn. 49)

41 **42** **41a** **111**

In the addition the already mentioned 'dimerization' of the acyl cyanides (Rn. 2), as well as the formation of enol esters (Rn. 3) rest upon the acylation potential of the acyl cyanides (cf. Section 5.1, Rn. 66). This is true also for the so-called cyanoacylations of aldehydes, whereby the cyano-group is finally incorporated into **112** as is shown in Rn. 50[1].

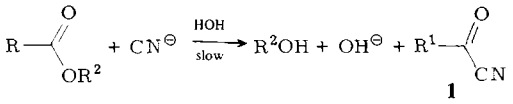
The reduction of **1** with BH_4 leads to the same type of product **112**, but with R = Ar. Here too intermediate cyanohydrin anion becomes acylated.

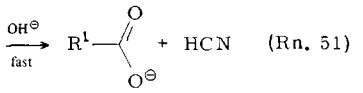


(Rn. 50)

1 **112**

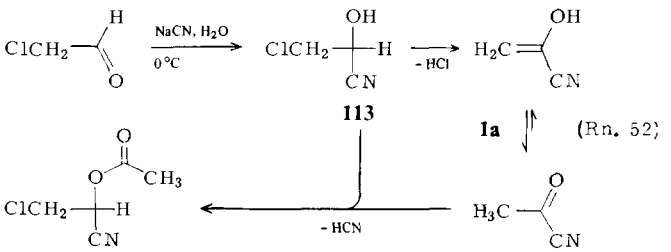
The cyanide-catalyzed ester hydrolysis examined in buffer solutions also proceeds *via* an acyl cyanide intermediate **1** which is quickly hydrolyzed[66b] (Rn. 51).





(Rn. 51)

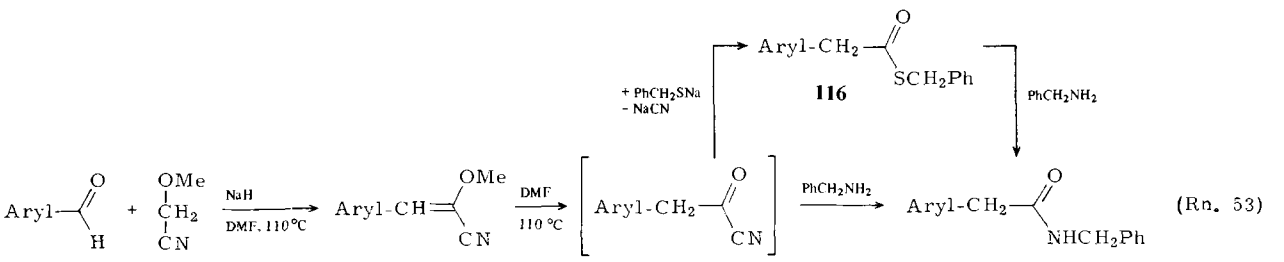
The hydrolysis of ethyl thiolacetate is also catalyzed by HCN[66b]. In the cyanide catalysis of the enzymatic acylation by means of acetyl coenzyme-A, acetyl cyanide was already assumed to be the effective intermediate[68]. Its powerful acylation potential is demonstrated by the reaction of chloroacetaldehyde with sodium cyanide in water. Here, formation of the intermediary cyanohydrin **113**, followed by HCl elimination (see Rn. 20) affords first **1a** ($R=CH_3$), which then acylates excess of **113**, so that finally 90% **114** can be isolated[69].



(Rn. 52)

114 (90%)

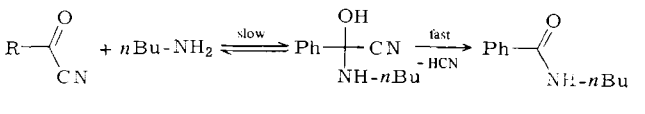
An intermediate acyl cyanide is also liberated from the enol ether **115**, with benzyl thioalcoholate. Since benzylamine is present at the same time it reacts either directly and/or *via* the thiolester **116** to form the end product, the amide **117**[70] (DMF = dimethylformamide).



(Rn. 53)

115 (81%) **117** (95%)

Amines such as *n*-butylamine cleave **1** ($R=Ph$) in ether according to a complex kinetic law. The main part of the reaction may proceed *via* the intermediate **118**[66c].

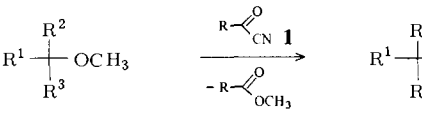


(Rn. 54)

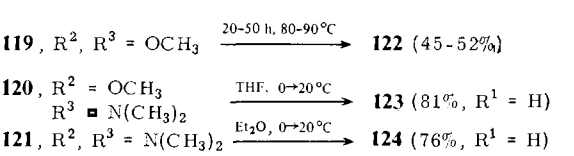
1, R = Ph **118**

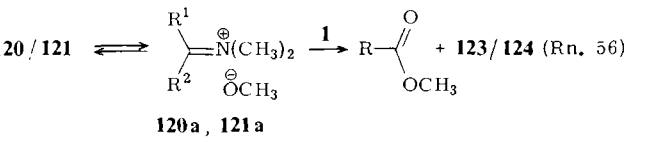
Since acyl cyanides are now readily accessible, their proposed use as mild acylating agents in peptide synthesis[67] should gain in importance.

The cleavage reactions of the acyl cyanides so far discussed utilize, almost without exception, the acylation products formed. Reaction 55 shows examples in which orthoesters **119**[71], amidoacetals **120**[72], and aminal esters **121**[72] exchange a methoxy-group for cyanide; the products **122—124** are also to be regarded as derivatives of acyl cyanides. In this way **1** acts as a convenient substitute for the otherwise necessary anhydrous hydrocyanic acid. The strongly exothermic reaction with **120** and **121** may proceed better *via* the equilibrated ion pair **120a** and **121a** according to reaction 56 than *via* intermediate *N*-acylation[72].



(Rn. 55)



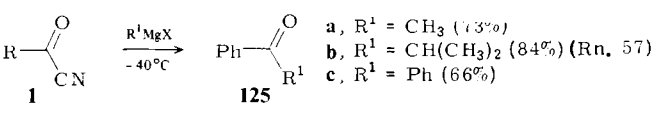


(Rn. 56)

120a, **121a**

4.4.2. Reactions with Organometallics, CH-Acidic Compounds, and Hydride Reagents

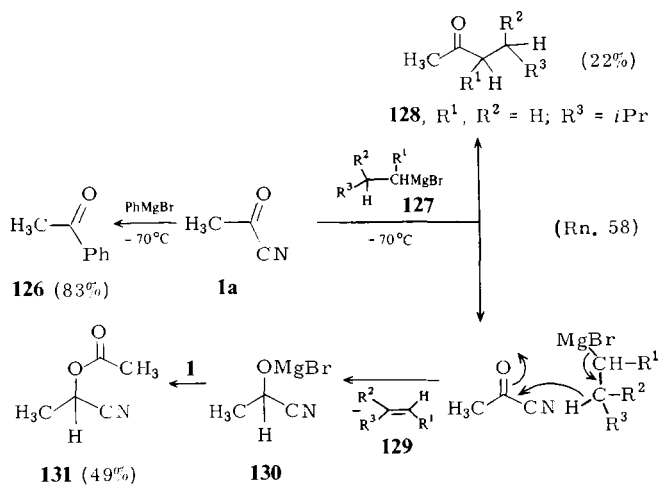
The well known reaction of benzoyl cyanide with phenyl magnesium bromide to give triphenyl acetonitrile or triphenylcarbinol[1] can generally be interrupted at low temperatures if carried out in a 1:1 stoichiometry with formation of the ketones **125**[73]. In the case of **125a** the substituents of the reactants can even be exchanged and thereby acetyl cyanide (**1**, ($R=CH_3$)) transformed into acetophenone **126**. Grignard compounds that are easily

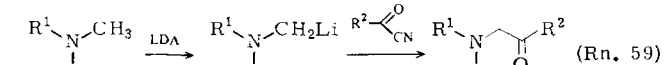


(Rn. 57)

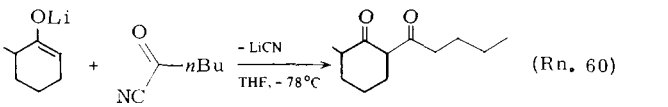
R = Ph

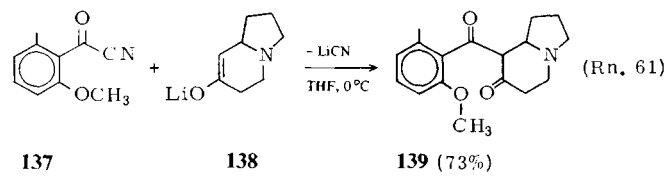
dehydrogenated[74] (*e.g.* **127**) yield with **1** (R = CH_3), α-acetoxypropionitrile **131** together with small amounts of ketone **128**. Obviously cyanohydrin salt **130** formed in addition to the olefin **129** is extremely rapidly acylated by the still available **1** to yield **131**[73]. The acylation of the lithium compounds **133** prepared from the nitrosamines **132** can be better stopped at the ketonic stage **134** by means of acyl cyanides, than by using acid chlorides or esters[75] (LDA = Lithium diisopropylamide).





The high reactivity of acyl cyanides at −78 °C also permits the clean *C*-acylation of kinetically generated enolates without causing *O*- or di-acylation, as the example **135** → **136** demonstrates[76].

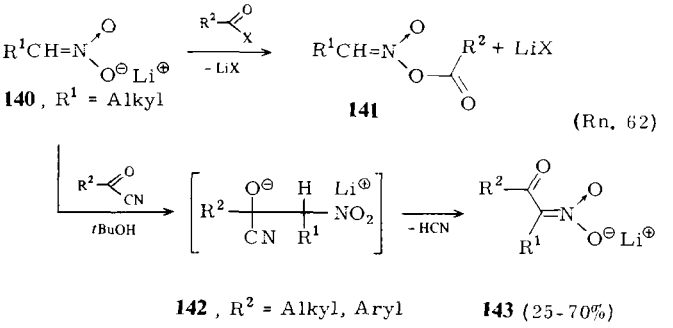




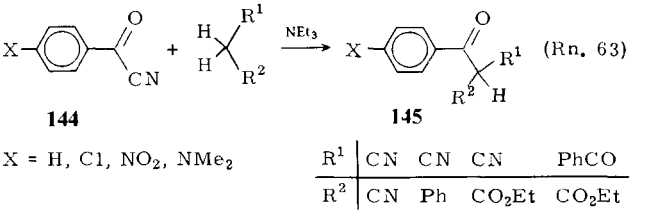
Even the aminoenolate **138**, which does not react in the desired way with other acylating agents, reacts smoothly with acyl cyanide **137** to give **139**[76].

Acyl cyanides prove also to be *C*-acylating agents for lithium salts of nitrocompounds **140**, while various other acylating agents produce only nitronic esters **141**.

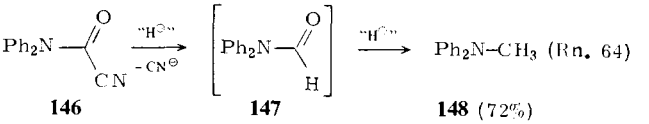
One would expect that the addition of acyl cyanide to the nitronic group is kinetically controlled, but that the adduct is in equilibrium with the reactants. These react finally *via* **142** with loss of HCN to give **143**. Such a reaction path rationalizes the fact that only primary nitroalkanes can be *C*-acylated[77] (Rn. 63). In contrast to benzoyl



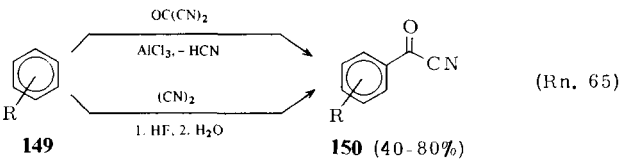
chloride, aromatic acyl cyanides **144** smoothly convert relatively acidic methylene compounds by *C*-acylation into the ketones **145**[78] (Rn. 63).



Acyl cyanides are reduced[1] by lithium aluminum hydride at both functional groups with preservation of their carbon skeleton. The carbamoyl cyanide **146**, however, suffers reductive cleavage to give **148**, presumably *via* the step **147**[79]—with formal acylation of the hydride ion (cf. the formation of **112** by BH_4^-[65b]).



As a special case the acylation of arenes **149** with carbonyl cyanide or dicyanogen under Friedel-Crafts conditions should be mentioned. In this case the reaction stops at the stage of the aromatic acyl cyanides **150** (cf., however, Section 4.2.1 Rn. 25!) which are thus also accessible by another pathway.

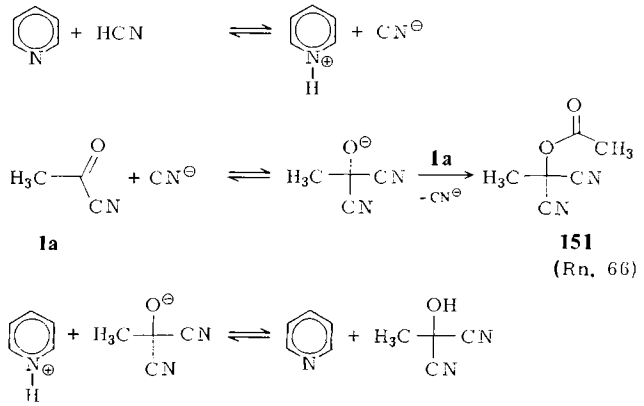


5. Dimeric Acyl Cyanides

5.1. Formation of Dimeric Acyl Cyanides

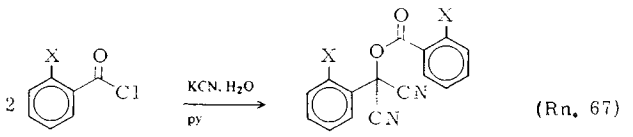
As mentioned in Section 2 acyl cyanides "dimerize" extremely easily[1]. A kinetic study of the particularly sensi-

tive acetyl cyanide **1a** in presence of HCN/pyridine has led to the following picture for the formation of **151**[81].



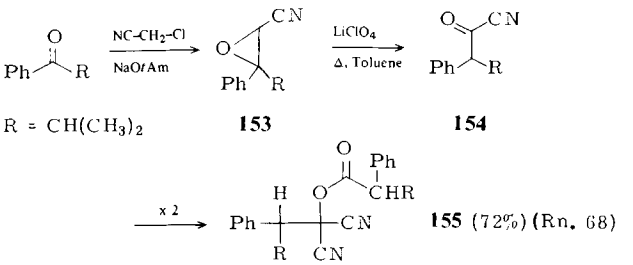
1a **151** (Rn. 66)

As a result of the strong cyanide ion catalysis, it is obvious that "dimers" from aromatic acyl chlorides and potassium cyanide do not only occur under phase-transfer catalysis (cf. Rn. 4g), but can also be isolated in presence of water/pyridine as the sole products **152**[82].



X = Cl, Br, OMe, NO_2 **152** (20–50%) (Rn. 67)

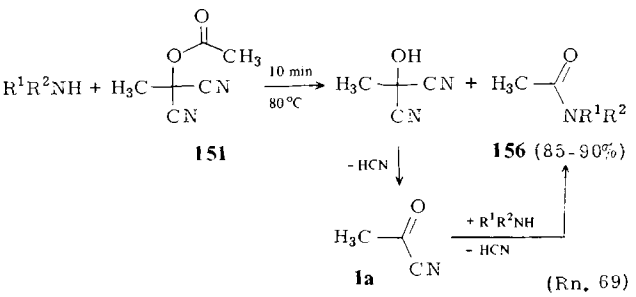
Evidently the hydrocyanic acid produced in a side reaction during the isomerization of **153** is sufficient to convert the acyl cyanide **154** largely into the dimer **155**[61] (cf. also Rn. 44).



R = $CH(CH_3)_2$ **153** **154** **155** (72%) (Rn. 68)

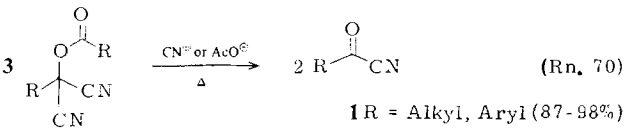
5.2. Reactions of Dimeric Acyl Cyanides

As has been known for a considerable time both acyl moieties of the "dimer" can be utilized[1] in the hydrolysis with dilute acids or bases as well as in the reaction with ammonia or phenylhydrazine. For instance, the reaction sequence 68 followed by hydrolysis is, therefore, suitable for transforming ketones into homologous carboxylic acids. While no ester interchange is observed with alcohols, aliphatic (not aromatic) amines react specifically to yield the amides **156**[83].



151 **156** (85–90%) **1a** (Rn. 69)

As was found recently, the dimeric acyl cyanides **3**, upon heating, can be smoothly converted by base into monomers[84] by reversing their formation as in reaction 66. Thus **3** is likely to gain in importance as a stable form for storing sensitive acyl cyanides.



1 R = Alkyl, Aryl (87–98%)

6. Summary and Prospects

The present review demonstrates that the reaction potential of acyl cyanides has been considerably extended during the past 25 years. This, however, can only now be fully utilized, as even sensitive (aliphatic) acyl cyanides have become easily accessible under very mild conditions (Scheme in Section 3). Acyl cyanides can be recommended as (selective) O-, S- and N-acylating agents under almost neutral conditions, as they require no auxiliary bases. Ambidentate enolate ions are obviously *C*-acylated in a largely specific way (Scheme 4 in Section 4.4).

All reactions with preservation of the C-framework lead at the same time to a C_1-extension of the respective carboxylic acids. In this manner nucleophiles can be made to attack one of the two functional groups, so that in the reaction with the CO-function substituted nitriles are produced (Scheme 2 in Section 4.2), while attack on the CN-group furnishes α-oxocarboxylic acid derivatives (Scheme 3 in Section 4.3). The directed, stepwise ring-closure with bifunctional nucleophiles transforms acyl cyanides into 5- and 6-membered heterocycles (Schemes 2 and 3).

The synthetic potential of the cyanotrimethysilane adducts as in reactions 8—11 has so far not been exploited, nor has that of the acyl cyanide enolic derivatives according to reactions 28—34 which are at present being studied in our laboratory.

The results of the Würzburg group presented in this review originate from the extensive and critical investigations of U. Hertenstein, H. Reichelt and R. Schaller[11]*. For the generous sponsorship of these studies we thank the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, and BASF, Ludwigshafen/Rhein (Germany).*

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Optimal Parameters in High Speed Liquid Chromatography (HPLC)

By István Halász* and Gerhard Görlitz

Dedicated to Professor Géza Schay on the occasion of his 81st birthday

After a decade, the first storm of development in high performance liquid chromatography seems to be abating. Providing the stationary phase and eluent are optimized, most routine analytical and semi-preparative separation problems require columns having between 1000 and 10000 theoretical plates. Commercial apparatus and columns completely satisfy these requirements. For many separation problems the efficiency of the columns on offer is greater than required. Since optimal (not maximal) separation is required with shorter analysis times, the column inlet pressure is increased in order to increase the eluent velocity, while at the same time reducing the column efficiency. The same result can be obtained by using shorter columns and lower pressures. Since inlet pressures of more than 100 bar are seldom required in routine analysis, the term "*high pressure* liquid chromatography" is a misnomer.—It is probable that difficult separation problems, where several 100000 theoretical plates are required, will be studied in the next phase of development. It can be shown using nomograms that such problems can be solved within acceptable time limits using inlet pressures of less than 500 bar. Further possible directions of development are indicated.

1. Introduction—The State of the Art

The theoretical and experimental foundations of high speed liquid chromatography (high performance liquid chromatography HPLC) were laid down in late 1960's[1-18]. The pioneers of this renaissance of classical column chromatography were almost all originally gas chromatographers and sought to apply to liquid chromatography (LC) the experience they had gained in gas chromatography (GC). The aim was to increase the efficiency, sensitivity and speed of analysis by a factor of about 100. Since the theory of band-broadening in chromatography does not depend upon whether the eluent is a gas or a liquid, the main difference between GC and LC was seen in the diffusion coefficients and viscosities. The solubility of the sample was another difficulty in LC. The eluent in GC is almost inert and there is practically no interaction between eluent and stationary phase. Eluent and samples in LC must—because of the solubility problem—be similar to each other, so that the heats of adsorption of the eluent and of the sample are of the same order of magnitude. The problems of instrumentation in LC were also overestimated at first. The breakthrough for the routine use of HPLC took place at the 5th International Symposium, Las Vegas, 1969[19]. The first commercial instruments were exhibited there, and significant advances in practical applications were described. The development thereafter was explosive. It became more and more obvious that the additional parameter, the eluent, represented not only a limitation, but also a new degree of freedom. The separation conditions, *i.e.* the relative retentions, for a single stationary phase (column) can be accordingly varied within wide limits. Relatively reproducible methods have been developed for the production of chemically modified phases and especially for reversed phases. The "balanced density"[20-22] and viscosity[23] methods have proved suitable for packing columns. Particles of sieve fractions 5μ—10μ have been shown to be optimal and are to be recommended in practice. The introduction of easily manipulated sample ports of variable volume was an important instrumental development, while the introduction of stepping-motor driven piston pumps which could deliver liquids at 0.1 to 10 mL/min at pressures of up to 400 bar made it possible to produce programmes for gradient elution accurately and reproducibly by mixing the eluent components on the high-pressure side. In the last few years noteworthy innovations in apparatus design have not occurred. Detectors which operate on novel principles would be desirable. All the detectors used until now in routine LC are concentration- and not mass/velocity-sensitive[24]. The constancy of the eluent rate of flow thus determines the accuracy and reproducibility of quantitative analysis.

Modern commercial instruments almost invariably utilize piston pumps driven by stepping or rotating disc motors so that the liquid flow rate is reproducible within ±0.5% to ±1.5%. Delivery is almost pulse-free and the pumps are easily controlled. The constancy of the flow-rate at low delivery rates, however, is significantly worse than the values quoted, which can cause difficulties when gradient elution is practised. Pulse-free elution delivery increases the working life of the column, on the one hand, and the sensitivity of the detector on the other, especially when a refractive index detector is used. Piston pumps suffer from the disadvantage that non-polar solvents, such as heptane, do not wet the pistons and that maintenance is not entirely free from difficulties. Membrane pumps are significantly more reliable and require less maintenance than piston pumps. The flow, however, is constant to only

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$\pm 1.5\%$ to $\pm 5\%$: pulsating delivery is also a disadvantage and it is necessary to smooth this out using a damper, whose dead-volume makes gradient elution difficult. These economically priced pumps are hardly suitable for gradient elution, because they are not driven by stepping motors, and are hence difficult to control. The optimal pump for modern HPLC has yet to be developed.

The introduction of the flame ionization detector (FID) enormously increased the effectivity and applicability of GC. This detector is sensitive to mass velocity and its noise level is extraordinarily low (about 10^{-12} A or 10^{-10} g carbon/s). Its response factor for hydrocarbons is roughly independent of chemical constitution and structure. A detection principle of similar quality has not yet been discovered for HPLC.

Differential refractometers or spectrometers (IR, UV, fluorescence) are the predominantly used detectors in modern HPLC. All are sensitive to concentration and their response factors are very dependant upon the substance. Apart from a few exceptions the noise level of such detectors lies in the range 10^{-6}—10^{-7} g/g eluent. The concentration of sample in the eluent, however, is seldom greater than 100 ppm at peak maximum.

The absolute and relative retentions of samples are a function of the column temperature. Experience has shown that around room temperature it is sufficient to hold the column temperature constant to within $\pm 1\,^{\circ}C$. This may not be sufficient for samples having excessively long retention times (large heats of sorption). Chromatographic columns are packed with heat insulating materials, and hence the conduction of heat radially is very limited. It is not sufficient, therefore, simply to "thermostat" columns externally, but is also necessary to pre-thermostat the eluent. Experience has shown that about 30 cm of coiled steel capillary tubing (internal diameter 0.25 mm, external diameter 1.6 mm) is sufficient to achieve the necessary constancy. The band-broadening caused by such a capillary is usually negligible in analytical work with columns >15 cm long and >4 mm internal diameter with particle sizes >5 μm. The heat exchanger can, in such cases, be placed between the sample port and the separating column. If optimal separation is of importance then the heat exchanger should be placed before the sample port. In this case, however, the whole path of the eluent (including the sample port) up to the column must be thermostatted.

2. The Separating Column

In the age of the microprocessor it is particularly necessary to emphasize the triviality that components of a mixture which are not separated in the column cannot thereafter be electronically "resolved". The separating column remains the principal item of the chromatographic apparatus. The chromatographic separation depends upon the varying migration velocities of the various components of the sample mixture through the sample column. These differences in migration velocity, *i.e.* in the relative retentions (α) result from the different distribution coefficients of the various components of the sample, between the eluent and the stationary phase. With the exception of exclusion chromatography, these distribution coefficients are thermodynamic quantities that depend upon the nature of the sample, of the stationary and of the mobile phase, as well as upon the temperature. Pressure is also a significant parameter in chromatography under supercritical conditions. The cardinal problem in chromatography is the selection of a suitable separation system. Here, the experience of the chemist is decisive.

Elution chromatography, strictly speaking, is not a separation process in the usual thermodynamic sense[25]. The components of a mixture are certainly separated from each other, but they are at the same time diluted by the eluent. This dilution effect (increase in entropy) is described in the kinetic theory of chromatography in terms of the relative band-broadening h, or the number of theoretical plates n[*].

To a good approximation, the separation (R) of two neighboring peaks[26] is:

$$R = \frac{\alpha - 1}{4\alpha} \cdot \frac{k'_2}{1 + k'_2} \cdot \sqrt{n_2} \qquad (1)$$

Since for two closely neighboring peaks α is approximately 1, and since R is proportional to $(\alpha - 1)$ on the one hand, and only to $\sqrt{n}$ on the other, α must first be optimized. In what follows it will be assumed that the relative retentions, α, have already been optimized. This is usually achieved in HPLC by adjusting the composition of the eluent. Experience has shown that five (or less) different stationary phases are sufficient for solving many of the separation problems.

Because of the favorable relative retentions it is usual to work routinely with columns that are at most 30 cm long. Difficult separation problems—*e.g.* in fields such as biology, biochemistry, pharmaceuticals, and petrochemistry—where plate numbers of more than 50000 are required and where capillary GC is not applicable, have hardly been tackled until now. Hereby, either the α values are small or the number of components to be separated, and hence the peak capacity required, is large. For this reason the evaluation of the optimal kinetic parameters will be discussed in this article. It will be assumed that the h-values are independent of the length of the column.

2.1. Column Packing

Without going into the details of this problem it need only be mentioned that sufficiently narrow sieve fractions for the production of columns are commercially available having stationary phase average particle sizes of between 5 and 30 μm. Such solid particles have a large surface area and are almost colloidal in size: packing methods described in the literature are thus empirical and not always properly reproducible. It is for this reason that the efficien-

[*] The commonly used symbols are tabulated in the list on p. 57. The most important parameters for HPLC (*e.g.* viscosity and diffusion coefficients) are still tabulated in CGS units. Consequently these units are overwhelmingly used in practice and in the literature.

cies of commercial columns vary so greatly. The efficiencies of such columns are often quoted in terms of plates per metre, which can be misleading. For example, when 25 cm columns are coupled together into longer columns, it often transpires that the plate number does not increase proportionally.

A simple quantitative method for the evaluation of packed columns will be described in this article.

2.2. Asymmetry Factor

The theory of chromatography assumes that eluted peaks possess a Gaussian distribution. Such peaks have, unfortunately, not yet been observed experimentally. The plate number is often calculated from the "mother"[23] peak, neglecting its leading and tailing edges. When a separation as far as the base line ($R = 1.5$) is required, which is a necessary condition for quantitative analysis, such methods are invalid. Asymmetrical peaks can be caused by strong interactions between the sample and the stationary phase and/or by instrumental or packing defects. If the asymmetry is attributable to the latter causes then the asymmetry factor (As)[23] decreases with increasing retention time. In this article asymmetry factors of between $As = 0.9$ and 1.2 will be assumed for capacity factors k' of between 1 and 2. This condition is fulfilled by good commercial columns.

2.3. The Particle Size of the Packing Material

The average particle size of a sieve fraction suitable for HPLC is a function of: 1. The method of measurement (optical, sedimentation, conductivity, Coulter counter, *etc*), and 2. The form in which it is reported (*i.e.* as number or as weight average). These methods require complicated equipment and a great deal of time, and can only measure the size of particles outside the column. They are unable to furnish information about the well-known problem of agglomeration during the packing of the column, which can lead to appreciable reduction in column efficiency.

We prefer to define the average particle size (δ) in the packed column using a chromatographic method[27]:

$$\delta = \sqrt{10^3 K_r} \equiv \sqrt{\frac{10^3 F \eta L}{r^2 \pi \Delta P}} \qquad (2)$$

For irregular particles the empirical factor of 1000 makes the value of δ agree well with the optically measured number-average particle size[27]. In our experience, a factor of 700 (instead of 1000) would be required in eq. (2) if the particles were spherical. We prefer, however, irrespective of the particle geometry, to define the particle size in terms of eq. (2) since δ is then defined in terms of the "price" (pressure drop) that has to be paid for a particular particle size. Values of δ approximately 15–20% larger are then computed for spherical particles than for irregular ones. Experience has shown that, independent of particle shape, the agreement between δ-values and the average particle diameters, d_p, quoted by manufacturers of commercial columns is acceptable[28].

The quality of a column is often described in terms of the dimensionless reduced plate height, h/δ. According to the definition of δ in eq. (2), smaller (better) reduced plate heights should be obtained using spherical particles. Surprisingly, however, experience has shown that the reduced plate heights obtained using spherical and irregular particles are not different[28,29].

The question of the advantages and disadvantages of spherical or irregular particles is often and exhaustively discussed. Some workers maintain that the quality and reproducibility of columns packed with spherical particles should be better. Others, hold the contrasting viewpoint that spherical particles are more easily displaced during packing. Possibly these effects depend more upon the dispersion of the sieve fraction than upon the geometry of the particles. At the present time, fractions are commercially available for HPLC that ought to be completely satisfactory. This applies not only to the dispersion of the sieve fraction but also to the reproducibility of the specific surface area and to the pore size distribution. Returning to the discussion concerning the geometry of the particles, only one thing seems certain: spherical particles are significantly more expensive.

The reproducible production of columns packed with particles larger than 4 μm (mostly smaller than 15 μm) has been mastered. This applies to columns packed with silica and alumina, as well as to those packed with chemically bonded phases. When operating short columns ($L = 10$ cm) with 5 μm particles the band-broadening resulting outside the column is, in many commercial instruments, comparable with that occuring within the column. Such columns are popular because of the high rates of analysis that can be obtained using them. As a result, the reduced plate heights obtained with these columns (5 μm) are significantly worse (larger) than columns packed with 10 μm particles. In other words, 5 μm ($L = 10$ cm) columns produce, under these conditions, fewer theoretical plates than 10 μm ($L = 20$ cm) columns. The pressure drop and rate of analysis are, however, larger for the former columns.

Columns packed with 3 μm particles were described five years ago[30] and are now commercially available. However, not only the analysis rate, but also the instrumental difficulties, the pressure drop, and the reduced plate height are large for such columns.

2.4. Simple Separation Problems

It will be assumed in what follows that the particle sizes, as is usual today, lie between 5 μm and 10 μm and that the HPLC separation is performed isocratically. About 10000 plates can be produced by a normal 30 cm column at the minimum in its h, u curve (*i.e.* at u_{min}). It can be calculated using eq. (1) that in the $k' = 1$ region, substances with relative retentions greater than 1.14 can be separated to the base line. In fact the α values are significantly larger than 1.14 for most routine separations in simple systems and, hence, the separations achieved are better than base line separations ($R > 1.5$). If a shorter column whose separating ability was sufficient for quantitative analysis ($R = 1.5$) were used then, if the other parameters were kept constant,

the analysis time would decrease and the detection sensitivity increase.

Instrumentally, it is easier to decrease the analysis time by increasing the linear velocity of the eluent, whereby the h-value increases. Then, not only the rate of separation but also the pressure drop increases, while the detection sensitivity decreases. The routine application of this method of decreasing the analysis time is certainly a significant reason for the frequent use of expensive high pressure pumps. Pumps which deliver 400 bar or more are unnecessary for most routine applications.

Experience shows that most everyday problems in HPLC can be solved using two lengths of column (*e.g.* 10 and 30 cm). The shorter column should, however, have a larger internal diameter (*e.g.* 6 mm) than the longer (*e.g.* 4 mm) in order to be able to neglect band-broadening outside the column.

Longer column working life and less wear and tear on the apparatus are further significant advantages of working with short columns and small pressure drops.

The quantitative computation of the optimal parameters for such short columns ($L \leq 30$ cm, $\delta \geq 5$ μm) is unnecessary since, as described above, commercial pumps have a sufficient pressure reserve.

2.5. Difficult Separation Problems

When the relative retentions of the substances to be separated are about 1.06 then approximately 50000 plates are required when $k' = 1$. Such plate numbers can be achieved either using longer columns or much smaller particles for the stationary phase. This also applies to the separation of multiple component mixtures that require a large peak capacity[31]. Finding the optimal conditions for the operation of such columns is an urgent task.

Whereas pressure drop and analysis times (or speed of analysis) were of subordinate importance with short columns, they become parameters of extraordinary importance for complicated separations. For such problems pressure drops are in the kilobar range and analysis times are measured in hours. Both are *reciprocal* functions of the linear velocity u of the eluent. How is the optimal velocity u established? The problems involved can be underlined by reference to gas chromatography and by comparing GC with HPLC.

2.6. Speed of Analysis and Pressure Drop in GC and in LC

Independent of the phase of the eluent, the speed of analysis in chromatography is characterized[32] by the number of theoretical plates generated per unit time ($n/t \sim u/h$). The necessary pressure drop, on the other hand, is proportional to the product $h \cdot u$, when a constant separating ability (number of plates) is required. It is meaningful, therefore, to plot the analysis time as a function of the pressure drop ($\sim h \cdot u$). Such a plot for peaks of similar capacity factors in typical GC and typical HPLC columns are illustrated in Figure 1. In order to allow direct comparison, both sets of axes are normalized with respect to the minimum in the h,u curve. It can be seen that for GC the speed of analysis reaches an upper limit at relatively low pressure drops. Speeds of analysis, which are barely affected by further increases in pressure drop, are achieved at relatively low pressures ($\sim h \cdot u$). It can, therefore, be taken as a rule of thumb that the optimal linear velocity u_{opt} is:

$$u_{opt} \simeq 2u_{min} \tag{3}$$

It can be seen, among others, from Figure 1 that the LC curve has not reached a limiting value even at 20 times u_{min}. For this reason there is no optimal velocity in the range of practical HPLC ($\Delta P < 600$ bar). With increasing pressure the speed of analysis is greatly increased.

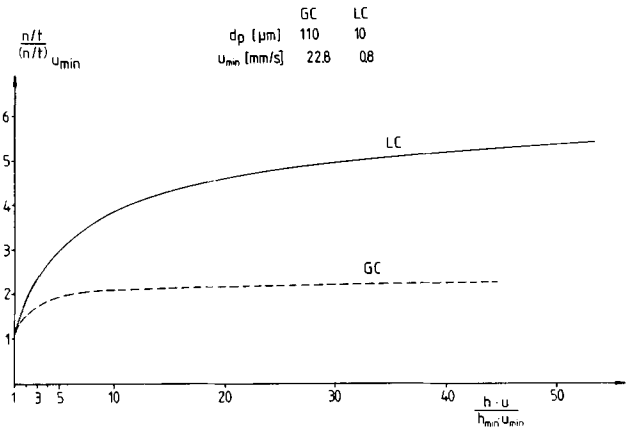

Fig. 1. Normalized velocity of analysis as a function of expense of analysis ($\sim \Delta P$). Normalization: N/t and $h \cdot u$ are normalized with respect to the values at the minimum of the h,u-curve. Column data for GC [33]: Conventionally packed column, $L = 200$ cm, internal diameter = 4 mm, 5% squalane on Chromosorb W, sieve fraction = 100–120 μm, carrier gas = N_2, 75 °C, sample = *n*-hexane; $k' = 1.51$, $h = 1.26 \times 10^{-2} + 8.3 \times 10^{-2}/u + 1.6 \times 10^{-2} u$ [h in cm and u in cm/s]. Column data for LC: $L = 10$ cm, internal diameter = 4.6 mm, Lichrosorb SI 100 (Merck), $\delta = 10$ μm, *n*-heptane, 25 °C, sample chrysene, $k' = 1.5$, $h = 23 + 4/u + 6.3u$ [h in μm, u in mm/s].

Whereas in GC it is usual to work with sieve fractions of 100 to 200 μm, experience has shown that in HPLC it is better to increase the speed of analysis by using much smaller particle sizes, than by increasing the speed of flow with longer columns.

Several investigations concern themselves with evaluating the optimal experimental conditions for LC[34-40]. The techniques suggested are mathematically complicated and not easy for experimentalists to manipulate.

A simple method which allows the graphical determination of optimal parameters had been developed and reported in 1977[41]. Its further development is reported here.

2.7. A Semiempirical Description of the Plate Height in HPLC as a Function of the Particle Size and the Eluent Velocity

The relative band-broadening h is a complicated function of many parameters. The most important, which will be discussed here, are: the velocity of the mobile phase (u), the particle size of the stationary phase (δ), the diffusion coefficient of the sample in the eluent (D_m), and the capac-

ity factor of the sample (k'). The last two parameters are themselves dependent upon the temperature. If the relative molecular weights of the samples lie between 75 and 300 (which is typical in separations of organic substances) then, to a first approximation, standard values of D_m can be adopted for particular values of the viscosity of the eluent (*e.g.* for $\eta = 0.4$ cP, $D_m = 3 \times 10^{-5}$ cm^2/s). For this reason we have taken the viscosity as a parameter, instead of the sample's diffusion coefficient whose exact value is usually unknown.

The h-value usually increases with increasing k'. For the sake of simplicity a value of $k' = 2$, which lies in the middle of the practical range, is assumed.

Using these boundary conditions, the value of h in HPLC can be described using the following semiempirical function of u and δ[42]:

$$h = a\delta + \frac{b}{u} + c\delta^2 u \tag{4}$$

where the constants a, b, and c depend upon the quality of the packing and the viscosity of the eluent η (*i.e.* upon D_m). As packing methods are improved, the values of the empirical constants in eq. (4) will decrease. It appears that the values of these parameters are independent of whether silica gel, aluminum oxide, or chemically bonded reversed phases are used as packing materials.

Two standard systems which correspond to columns packed by state of the art methods are mathematically described in what follows. For eluents of low viscosity, such as *n*-heptane, dichloromethane, acetonitrile, methanol *etc.* (η between 0.4 and 0.6 cP), the following equation applies:

$$h = 1.5\delta + \frac{6}{u} + \frac{\delta^2}{16}u \qquad \text{"formula I"} \tag{5}$$

where the usual HPLC units of measurement are used, *i.e.* h and δ are expressed in μm and u in mm/s. The constants 1.5, 6 and 1/16 of course have the corresponding dimensions.

For a more viscous eluent, such as a mixture of water and acetonitrile, or water and methanol (η between 0.7 and 1.5 cP), the following equation applies:

$$h = 2\delta + \frac{3}{u} + \frac{\delta^2}{8}u \qquad \text{"formula II"} \tag{6}$$

Equations (5) and (6) correspond to the experimental results if

1) the particle size δ of the stationary phase lies between 3 and 30 μm;
2) the linear velocity of the mobile phase is less than $20u_{min}$;
3) the relative molecular weight of the sample is less than 300 and its capacity factor k' is approximately 2.

Both these formulae are approximations. They are, however, easy to manipulate and require only easily measured quantities. They can be used, for example, to judge the quality of columns that have been packed with different materials. Use of eq. (2) to determine the particle size in eqs. (5) and (6) enables one to be independent of manufacturers' data. It should be mentioned that calculated and measured values will only agree if extra-column band-broadening is negligible.

3. HPLC Optimization

The most important parameters in the optimization of an HPLC analysis are: α, D_m, k', η, L, n, t_0, ΔP, and δ; other parameters (*e.g.* u, R, h, n/t_0 *etc.*) can be derived from them. Optimal relative retentions α are assumed. The diffusion coefficient D_m, the viscosity of the eluent η, and the capacity factor k' are given standard values in eqs. (5) and (6). The remaining five parameters are not independent of each other. The column length L can be eliminated, between eq. (2) and:

$$u = \frac{L}{t_0} = \frac{F}{r^2 \pi \varepsilon_T} \tag{7}$$

where ε_T is the total porosity, it follows that

$$L = \delta \sqrt{\frac{t_0 \Delta P}{10^3 \eta \varepsilon_T}} \tag{8}$$

so that eq. (4) with $h = L/n$ can be rearranged using the remaining four parameters to give:

$$n = \left[a \sqrt{\frac{10^3 \eta \varepsilon_T}{t_0 \Delta P}} + \frac{10^3 b \eta \varepsilon_T}{\delta^2 \Delta P} + \frac{c\delta^2}{t_0} \right]^{-1} \tag{9}$$

Figures 2 and 3 show the plate number as a function of particle size for various values of t_0 and ΔP using formula I [eq. (5)] and formula II [eq. (6)]. This is of significance because, as already discussed, analysis time and pressure drop are limiting parameters in difficult separations.

In Figure 2, where a "low viscosity" eluent ($\eta = 0.44$ cP), a porosity which is typical for silica gel ($\varepsilon_T = 0.82$), and the validity of formula I [eq. (5)] are assumed, the breakthrough time remains constant, 5 min, in all three cases.

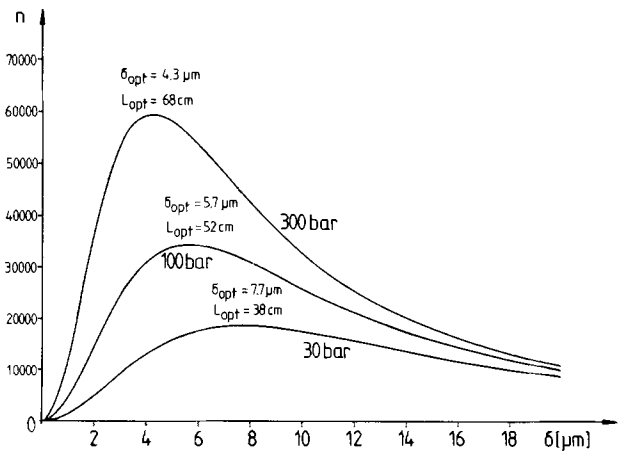

Fig. 2. Number of plates as a function of the particle size for "low viscosity" eluents at $t_0 = 300$ s and constant ΔP.
$h = 1.5\delta + 6/u + \delta^2 u/16$, $\eta = 0.44$ cP, $\varepsilon_T = 0.82$.

Figure 3 is valid for a "high viscosity" eluent ($\eta = 1.2$ cP), and for a porosity ($\varepsilon_T = 0.70$) which is typical for a chemically modified phase. Formula II [eq. (6)] was used and a pressure drop of $\Delta P = 100$ bar assumed in all cases. All the curves in both figures pass through a maximum, *i.e.* under these conditions the maximum number of plates can only be achieved with a particular particle size. The column length which corresponds to the optimum can be calculated from eq. (8).

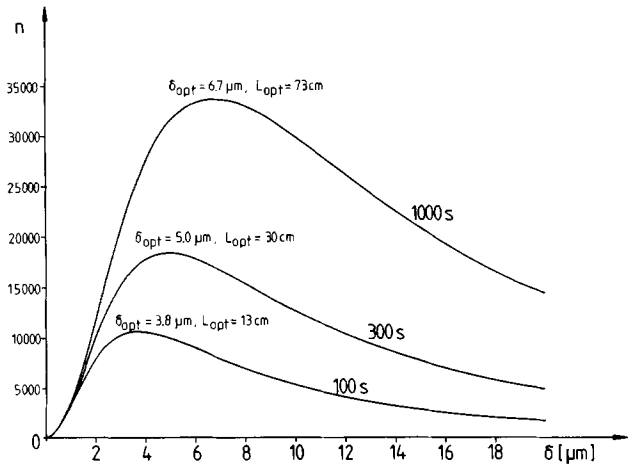

Fig. 3. Number of plates as a function of the particle size for "high viscosity" eluents when $\Delta P = 100$ bar and t_0 is constant.
$h = 2\delta + 3/u + \delta^2 u/8$, $\eta = 1.2$ cP, $\varepsilon_t = 0.70$.

As can be seen from Figure 3 it is possible to generate *ca.* 35000 plates within 1000s for t_0, with a pressure drop of only 100 bar, using a system which is typical for reversed phases. The optimal particle size is about 7 µm and the column is 73 cm long. Separating ability, which is the factor of interest to the chromatographer, only increases as the square root of the number of plates [eq. (1)] and for this reason a loss in n of 10—20% is acceptable in practice. If such a reduction is accepted then δ can be varied over the range 4—10 µm. When δ is changed, the corresponding column length must also be, according to eq. (8). As is evident from this example (cf. Section 2.7), this form of optimization requires only a rough gradation of particle size and column length. For the user this means that he can work optimally under many different sets of conditions by choosing from a very few types of column.

In the appendix it is shown that the maximum in the n,δ-curve (ΔP and t_0 constant) can also be derived mathematically. All parameters which apply to the maximum will be designated with the subscript "opt". The equations for calculating δ_{opt}, L_{opt}, and n_{opt} can be found in the appendix [eqs. (A6) to (A8)]. If L_{opt} in eq. (7) is divided by t_0, and t_0 and ΔP are eliminated using the equation for δ_{opt} (A6), a value is obtained for the linear velocity which corresponds to the maximum of the n,δ-curve.

$$u_{opt} = \frac{1}{\delta}\sqrt{\frac{b}{c}} \qquad (10)$$

This velocity is identical to the minimum in the h,u-curve calculated from eq. (4). The velocity $u_{opt} = u_{min}$ can be calculated for "low viscosity" eluents using formula I:

$$\delta u_{min} \approx 10\ [\mu m\ mm/s] \qquad (11)$$

and for "high viscosity" eluents using formula II:

$$\delta u_{min} \approx 5\ [\mu m\ mm/s] \qquad (12)$$

From our arguments we can establish:

1) For a given pressure and analysis time, maximal efficiency can only be achieved when L and δ are chosen such that one is working at $u_{min} = u_{opt}$.

2) The maximal number of plates n_{opt} is proportional to the square root of the pressure and the analysis time.

3) The optimal particle size decreases with increasing pressure [$\delta \sim (\Delta P)^{-0.25}$], and increases with increasing analysis time [$\delta \sim t_0^{+0.25}$].

Working at u_{min} has the additional advantages:

a) The relative band-broadening h hardly varies as k' changes. In contrast, at eluent velocities significantly greater than u_{min} (*e.g.* $u > 5u_{min}$) the h value increases rapidly with increasing k'.

b) Since the relative band-broadening is minimal at u_{min}, it follows that peak height is maximal. This is of particular importance for trace analysis.

c) The working life of the column is extended because of the lower pressures required.

d) At fixed particle size the speed of analysis increases with increasing linear velocity of the eluent (cf. Fig. 1). When L and δ can be freely chosen, the maximum speed of analysis can, quite unexpectedly, be achieved at $u_{min} = u_{opt}$. This would seem, at first sight, to require an unacceptably large stock of different columns. That in practice just a few columns are sufficient will be shown using a nomogram (see Section 4).

Optimal Speed of Analysis

The speed of analysis decreases with increasing retention. The inert sample n/t_0 is always referred to here. Furthermore, ΔP and n are taken as required boundary conditions. If eq. (9) is solved for t_0 [eqs. (A10)—(A13)], then n/t_0 can be calculated as a function of δ [eq. (A15)]. Examples of such curves are shown in Figures 4 and 5.

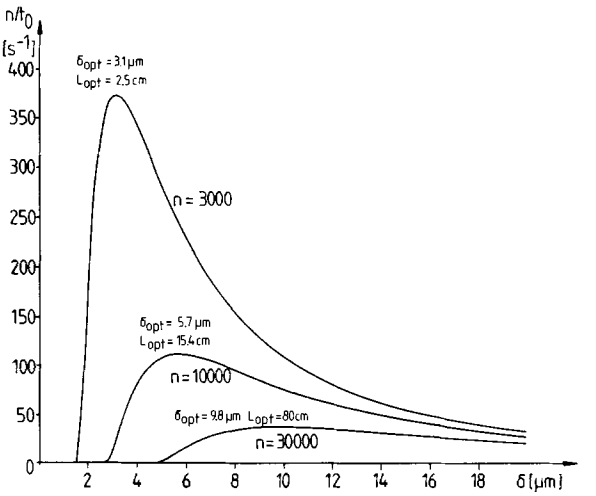

Fig. 4. Speed of analysis as a function of particle size for "low viscosity" eluents at $\Delta P = 30$ bar.
$h = 1.5\delta + 6/u + \delta^2 u/16$, $\eta = 0.44$ cP, $\varepsilon_t = 0.82$.

Once again it is evident that optimal working conditions—*i.e.* here the maximal speed of analysis—can only be achieved using a particular particle size and column length, which are determined by the chosen plate number and pressure drop.

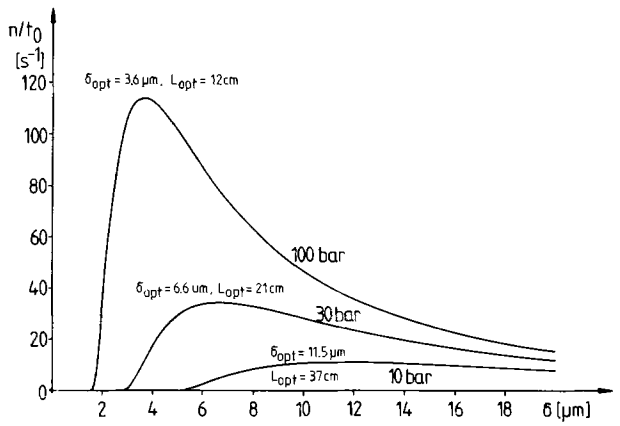

Fig. 5. Speed of analysis as a function of particle size for "high viscosity" eluents at $n = 10000$.
$h = 2\delta + 3/u + \delta^2 u/8$, $\eta = 1.2$ cP, $\varepsilon_t = 0.70$.

It can be seen from Figures 4 and 5 that for a given ΔP there is a minimum particle size below which it is impossible to obtain the required plate number, no matter what the speed of analysis. The sharp increase in n/t_0 at small values of δ can be explained as follows. On the one hand, according to eq. (11) u_{min} increases as δ decreases and, on the other, it follows from eq. (4) that:

$$h_{min} = \delta(a + 1.22) \approx \delta(a + 1) \qquad (13)$$

h_{min} is thus a linear function of δ. At the same time, the permeability K decreases as the square of δ. Taken together these phenomena have the effect that for a given ΔP there is a particular number of theoretical plates which it is no longer possible to generate below a certain minimum particle size.

It can be seen from Figure 5 that the number of theoretical plates required for routine analysis can be generated speedily and at a relatively low pressure drop. Take, for example, a C_{18} reversed phase and an H_2O/CH_3OH mixture with a high viscosity of 1.2 cP, if 10000 theoretical plates are required: for $\Delta P = 30$ bar the inert peak is eluted after 5 min. The column is, in this case, *ca.* 21 cm long and packed with 6.6 µm particles. It can also be seen that such an optimal separation can be approached using particles varying in size from 5—10 µm. The column length must then be increased with increasing δ. This example also illustrates the fact that the delivery pressure demanded of the pump is often far too high. Working at high pressures increases the cost of the apparatus, while the working-life of the column is decreased.

Eq. (A15), which describes the $n/t_0,\delta$-curve, is difficult to handle explicitly. It is possible, however, to show numerically that, for given values of n and ΔP, the maximum of n/t_0 is produced at u_{min}. When the shape of the $n/t,h\cdot u(\sim\Delta P)$ curves (Fig. 1) are considered, in view of the steep increase in h_{min} and u_{min} this result seems very improbable. This apparent contradiction can be resolved using a simple model.

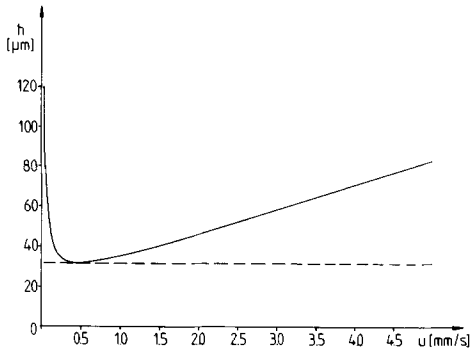

Fig. 6. h,u-Curves for a real and for a hypothetical (broken line) HPLC column.
Real Column: $\delta = 10$ µm, $\eta = 1.2$ cP. The solid curve was calculated using formula II [eq. (6)].

Consider a hypothetical HPLC column where the value of h is independent of the velocity and is always equal to h_{min} as described in eq. (13), and shown by the broken line in Figure 6. The relationship between the speed of analysis and the particle size can be deduced as follows:

1) Since the number of plates n remains constant and $h = h_{min}$ is proportional to δ [eq. (13)], the column length must also remain proportional to $\delta (L \sim \delta)$.

2) If ΔP is constant then u is proportional to δ^2 and inversely proportional to $L (u \sim \delta^2/L)$. Because $L \sim \delta$ it follows that $u \sim \delta$.

3) The breakthrough time of the inert peak ($t_0 = L/u$) is thus independent of the particle size.

Since n was taken as a constant, the speed of analysis n/t_0 must also be independent of δ and remain constant.

Thus the speed of analysis in this hypothetical column is independent of particle size of the stationary phase and linear velocity of the mobile phase (n and ΔP are constant).

The value of h in a real column is, except at u_{min}, always larger than h_{min}. Since $n/t_0 \sim u/h$, larger values of h imply lower speeds of analysis.

If the plate number and pressure drop in the column are taken as boundary conditions then the maximum speed of analysis will be achieved at u_{min}. Column length and particle size must, of course, be open to choice.

4. Graphical Determination of the Optimal Parameters

The equations for δ_{opt}, L_{opt}, and n_{opt} [eqs. (A6)—(A8)] can be transformed so that n_{opt} appears as a function of δ_{opt} and another parameter (either ΔP_{opt}, or L_{opt} or $t_{0,opt}$). These relationships [eqs. (A16)—(A18)], can be used to construct nomograms having the axes δ, n, ΔP, t_0, and L. Other parameters which can be deduced from these values are u_{opt}, h_{min}, and n/t_0. These are simply a function of δ and can accordingly be represented along an axis parallel to the δ axis and are added below the nomogram. It must be taken that 1) the particle size is that defined in eq. (2), 2)

the h,u-curve follows eq. (4) and can be explicitly described using either eq. (5) or eq. (6), 3) standard values are assumed for the viscosity of the eluent η and for the total porosity ε_T.

Good packing technique is assumed in eqs. (5) and (6): a good reproducible packing technique is available for columns having internal diameters of *ca.* 2 to 8 mm, lengths of 10 to 50 cm, and particle sizes ranging from 3 to 30 μm. Such columns should, furthermore, be capable of being coupled in series without loss in h-values.

The nomogram for "low viscosity" eluents is reproduced in Figure 7 and that for "high viscosity" eluents in Figure 8. These nomograms cover a wide range, *e.g.* particle sizes up to 100 μm and plate numbers up to 10^6. The portions of these diagrams which apply and are of interest in present day HPLC are reproduced in Figures 9 and 10. The values of the parameters held constant in construction of each nomogram are included in the figures.

Two of the five parameters (coordinate axes) may be chosen arbitrarily. An optimal combination of those remaining can then be read off the nomogram.

The silica gel/dichloromethane system—with a separating capacity of 100000 plates—is required for the relative retentions involved in a particular separation problem.

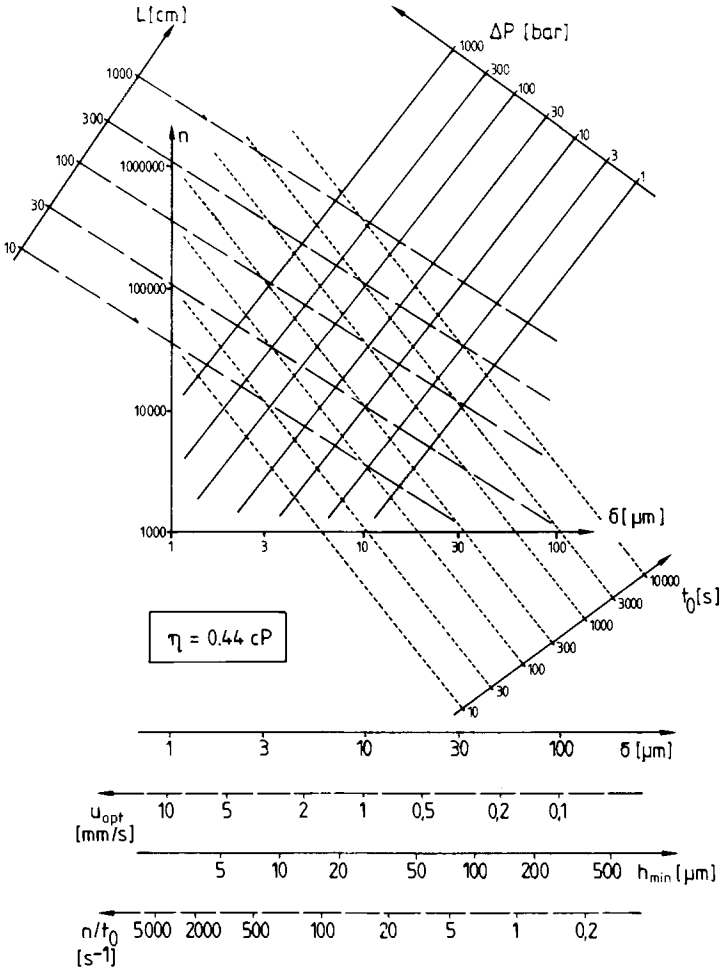

Fig. 7. Nomogram: Optimal parameters for "low viscosity" eluents, *e.g.* for the system silica gel/dichloromethane.
$h = 1.5\delta + 6/u + \delta^2 u/16$ [eq. (5)], $\eta = 0.44$ cP, $D_m \approx 3 \times 10^{-5}$ cm²/s, $\varepsilon_t = 0.82$.

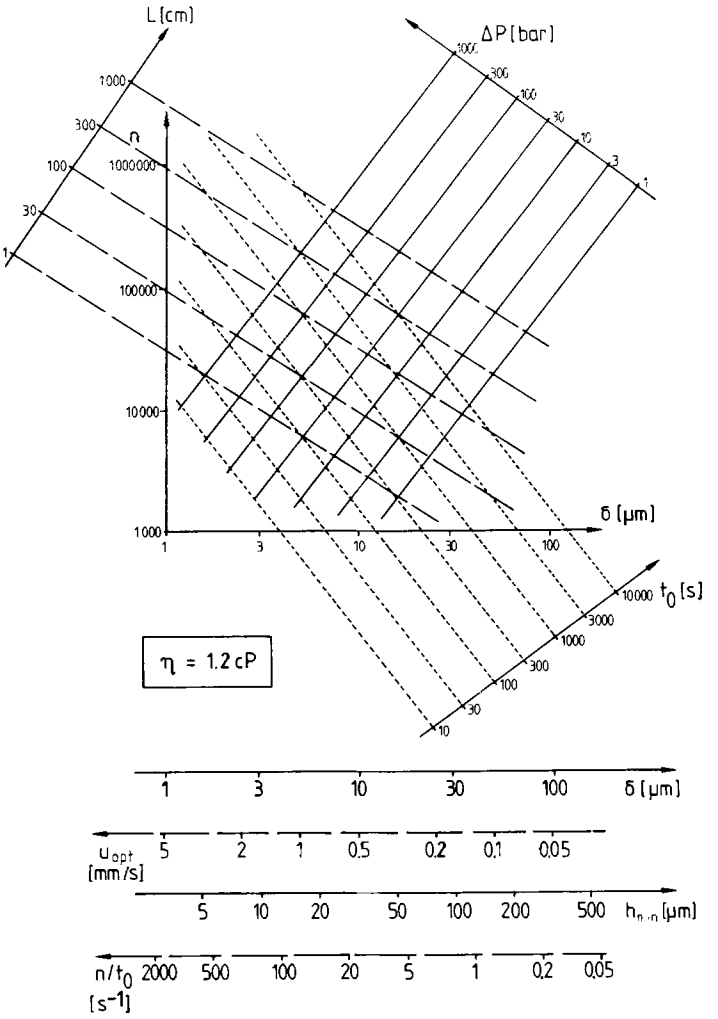

Fig. 8. Nomogram: Optimal parameters for "high viscosity" eluents, *e.g.* for the C_{18}-reversed phase/methanol-water system.
$h = 2\delta + 3/u + \delta^2 u/8$ [eq. (6)], $\eta = 1.2$ cP, $D_m \approx 1.5 \times 10^{-5}$ cm/s, $\varepsilon_t = 0.70$.

This is accomplished, in the first instance, by using a 50 cm long column (or two 25 cm columns in series). From the nomogram in Figure 7 it can be seen that a packing of *ca.* 2 μm (1.84 μm) particles and a pressure drop of almost 3000 bar (2850 bar) are required. The values in brackets were calculated using the relevant equations [(A 17) and (A 16)]. Such conditions are not realizable with present day techniques, nor are they to be recommended in principle[42]. The otherwise excellent values for $t_0 \approx 1.5$ min [93.8 s from eq. (18)] and hence $n/t_0 = 1070$/s are thus of theoretical interest only.

Since the plate value required in the above separation problem is $n = 100000$, it is necessary to insert the maximum available pressure as the second selected parameter. A maximum pressure of 300 bar can be reached, without problems, using modern commercial instruments. When $n = 10^5$ and $\Delta P = 300$ bar, the following values can be read off the nomogram: $\delta \approx 5.7$ μm, $L \approx 150$ cm, $t_0 \approx 900$/s, and $n/t_0 = 110$/s. These parameters seem acceptable. Whether the detection limits for the separated peaks are adequate remains a matter which can be most rapidly checked by experiment. As t_0 and k' increase, the peak height and the sensitivity of the analysis decrease. It can follow from this

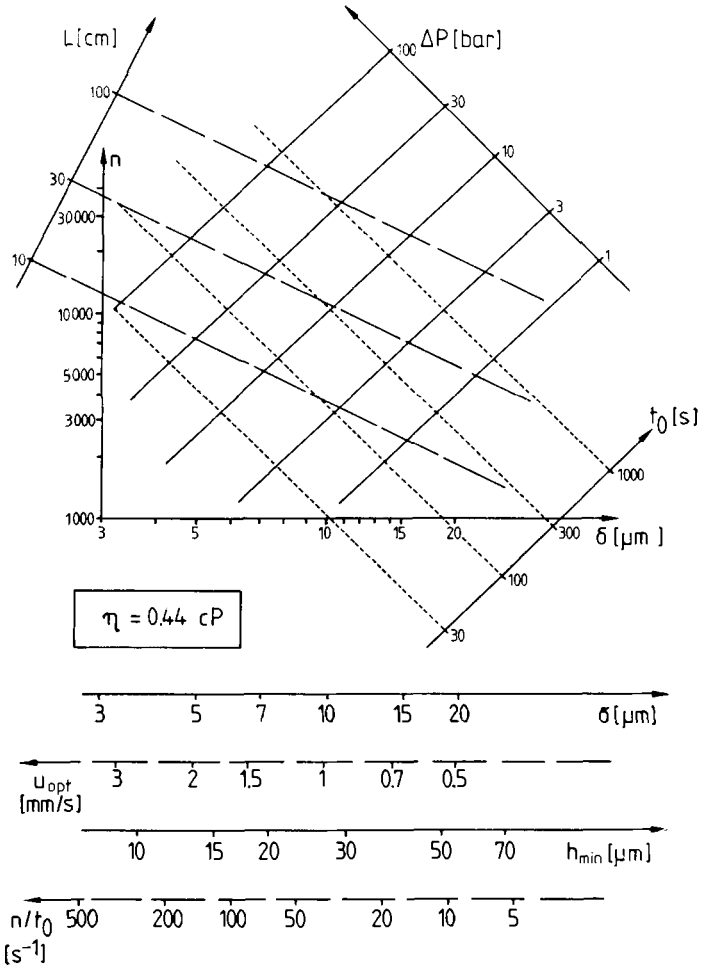

Fig. 9. Detail from nomogram in Fig. 7 ("low viscosity" eluent).

that a smaller value of t_0 together with n = constant must be taken as the selected parameter to be inserted into the nomogram.

The big advantage of the graphical representation is that it can be quickly ascertained whether a problem is soluble with present day techniques, what are the critical parameters, and what compromises must be made.

Several everyday analysis problems will now be discussed in terms of Figure 10. Here, a chemically modified phase, such as a C_{18} reversed phase, will be taken as the stationary phase, and a relatively viscous eluent ($\eta = 1.2$ cP), *e.g.* H_2O/CH_3OH. It can be shown once again that, in general, significantly lower pressures are necessary than are normally presumed and used.

With a required plate number of 10000 and a column length of 15 cm as the chosen parameters it can be read off the nomogram in Figure 10 that $\delta \approx 5$ μm and $\Delta P \approx 60$ bar are required. For an analysis time $n/t_0 = 70$ s an inert peak requires 2.5 min to breakthrough.

If the separation problem is simpler, so that $n = 5000$ is sufficient, then taking $\delta = 10$ μm, the following values can be read off from Figure 10: the column length remains almost constant ($L \approx 16$ cm), the analysis-time is approximately doubled ($t_0 \approx 5.5$ min and $n/t_0 \approx 15$/sec), while the pressure drop sinks to 7 bar.

These problems show that our nomograms (Figs. 7–10) provide a rough guide for the determination of optimal parameters. Two column lengths of 10 and 25 cm and two sieve fractions of $\delta = 5$ and 10 μm, respectively, suffice for the majority of problems. It is necessary to be able to connect the columns in series without raising the h-value.

If our suggestions are followed then perhaps twice as many columns should be stocked as has been usual up to now. This small increase in expenditure, however, produces the advantages of optimization. When working with the optimal parameters, pressures of more than 150 bar are seldom required. Cheaper, simpler and more reliable instruments can, therefore, be used for routine analysis. This applies not only to the pumps but also, to the same extent, to the injection ports *etc.* Although the manufacturers of chromatographic apparatus are perfectly willing and able to offer such components, there seems to be no demand for them at the moment.

Can it be a question of prestige? This must be considered since it is known that the working life of columns and, therewith, the reproducibility of analysis is significantly increased by careful use.

In order to avoid misunderstanding it should be mentioned that the large instruments, indispensable for the development of new methods, research, and the solution of complex problems, are not to be included in this stricture. When such problems are to be solved then the limits can be estimated quickly from the nomograms in Figures 7 and 8.

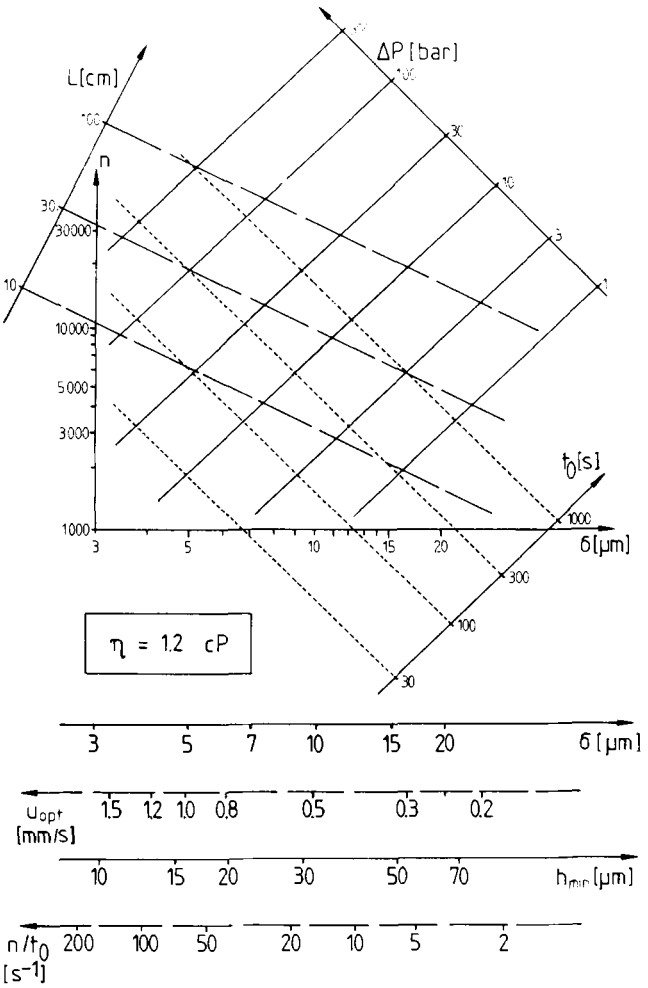

Fig. 10. Detail from nomogram in Fig. 8 ("high viscosity" eluent).

The necessary condition for the construction of the nomogram was isocratic elution (constant temperature, constant pressure and eluent composition). It should be mentioned that some of the problems which are at present solved using gradient elution can also be tackled isocratically. When computing the analysis time for a gradient elution the time required for column-regeneration should not be omitted.

5. Conclusions and Outlook

A short review of present day techniques with respect to instrumental difficulties in high speed liquid chromatography was followed by a comparison of the establishment of optimal separation conditions in gas and in liquid chromatography. Here it was shown that the optimal linear velocity is obtained at the minimum in the h,u-curve and that this occurs when a maximal plate count with limited ΔP and t_0 is aimed at, as well as when the maximal speed of analysis for a particular plate number and a limited pressure is the aim. Other advantages of working at u_{min} were discussed. We have developed nomograms which relate the parameters: plate number (n), particle size (δ), pressure drop in the column (ΔP), breakthrough time of the inert peak (t_0), and column length (L). Two of these parameters can be arbitrarily chosen and an optimal combination of the remainder read off. Since the values of u_{opt}, h_{min}, and n/t_0 are determined by the value of δ, these values can be determined using subsidiary axes below the nomogram. The viscosity of the eluent (diffusion coefficient of the sample) has a significant effect on the optimal parameters; in contrast, the particular kind of stationary phase has a much smaller effect. Nomograms were constructed for two typical systems and their possible uses were illustrated by using examples of simple and complicated separation problems. It turns out that significantly lower pressures can be used to solve routine problems than is often accepted. In conclusion we would like to survey some interesting possible directions of development.

When optimal conditions ($u = u_{min}$) are employed, the speed of analysis (*i.e.* the number of plates generated per unit time) increases approximately quadratically with decreasing particle size. Currently, columns packed with 10 μm or 5 μm particles are generally used. Recently, however, columns packed with 3 μm particles have become available. Here, the increase in speed of analysis must be paid for with the solution of new problems which arise. As the particle size is decreased the colloidal region is approached. The probability of coagulation will, consequently, be greater, the packing of the columns more difficult, their reproducibility less and their working-life shorter. With decreasing particle size, column length is decreased when constant plate numbers are required. If the column diameter remains unchanged then the peak volumes will be smaller and the cell volume of the detector must be decreased (to about 1 μL). The construction of such cells without decreasing sensitivity presents difficulties. It is worth mentioning that with 5 μm particles (column $L = 10$ cm internal diameter = 4 mm) most commercial instruments can only realize a fraction of the possible efficiency because of extra-column band-broadening.

Packing 1 mm internal diameter columns is difficult, but not impossible. The instrumental problems mentioned previously (sample application, cell volume) also occur here. Use of such columns can only be recommended when the amount of sample available is extraordinarily small or the optimal eluent very expensive.

Packed capillary columns show advantages for gas chromatography in that, compared to "classically" packed columns of the same particle size, they have a similar efficiency with a *ca.* 10 times greater specific permeability. Since significantly higher sheer forces are found in liquid chromatography, the reproducible production of such columns is more difficult and their working-life shorter. In our experience, the increased permeability, if it occurs at all, is significantly less than that found in gas chromatography. The low peak volumes produced here also occasion the previously mentioned instrumental problems.

It can be deduced theoretically (and demonstrated experimentally) that open tubular columns—also known as capillary columns—are only competitive with conventionally packed columns when their internal diameter is about 10 μm. In the literature the band-broadening of the inert peak is chiefly discussed. It is well known, however, that, on the one hand, because of sheer forces an even coating of stationary phase is extraordinarily difficult to achieve and, on the other, that the band-broadening of a retarded substance compared to that of an inert peak increases more rapidly than is the case with packed columns. Because of the very small sample volumes, cell volumes in the nanolitre range are required, and reliable pumps with low delivery rates are necessary. Capillary columns have advantages when the amount of sample is limited and the eluent is expensive. The technical difficulties, however, make it unlikely that this type of column could be made available in the near future for routine work.

Conventional columns up to 50 cm long can be packed satisfactorily using present techniques. When higher plate numbers ($n > 100000$) are required for difficult separations, then the minima of the h,u-curves are displaced to lower velocities and the ascending branch of the curve becomes steeper. Since these minima decrease with decreasing capacity factor, the speed of analysis also decreases rapidly. In such cases the analysis time soon becomes intolerably long. If columns coupled together in series to give an effective length of several meters are used, a new packing technology must be developed.

The separation of crude oil fractions, natural product extracts *etc.* is often difficult, because the polarity range of the individual components is large. Such complicated mixtures can be pre-separated by use of the extrographic method of separation (for extrography see [46]) (Samples of from about 30—250 g can be pre-separated within about 3 h). The fractions thus obtained can then be further separated by retentive- or by exclusion-chromatography.

If only a fraction of the components in the mixture is required then the technique column switching can be used, employing several stationary phases and diverse eluents; this can be viewed as an *in situ* sample preparation. In the case of multiple analyses, such as are undertaken in the fields of biochemistry and pharmacy, the time of analysis can be significantly shortened.

In liquid chromatography the internal diameter of a packed column can be increased to 50 mm or more, without significantly decreasing efficiency. In preparative separations, the amount of sample per unit amount of stationary phase is very often increased and the separation occurs according to the principles of displacement chromatography and not to those of elution chromatography. By proper choice of conditions remarkable purities and yields can be attained.

In the last few years it has become possible to record the UV/VIS spectrum as a function of time using diode array detectors. The absorption at more than 500 wavelengths can be simultaneously and repeatedly recorded at a frequency of 5 sec^{-1} or more, and stored. The necessary data processing makes such instruments expensive and the software on offer is not optimal. The optimal wavelength for routine analysis can be quickly established. If several components of differing and known spectra are hidden under a peak they can be estimated quantitatively. Very rapid identification of separated peaks is possible since a particular spectrum can be recalled at any time. If the analysis time of an abnormally complicated mixture is several hours and if the absorption maxima of the components have different wavelengths, such a detector is almost irreplaceable.

Most of the substances separated by exclusion chromatography have high molecular weight. Because of the small interdiffusional coefficients, band-broadening is significantly greater than is usual in retentive chromatography. Significantly better separations can be obtained here, without instrumental difficulties, by using particle sizes which are significantly less than the 10 μm usual today.

The separation and/or identification of single components (or groups) often requires multidimensional analysis. High speed liquid chromatography is being increasingly coupled with mass-, infrared- or nuclear resonance-spectroscopy. "On-line" coupling is, without question, quicker and more elegant. It is also instrumentally more taxing. Since the collection of HPLC fractions is simple, it is necessary to establish for each case whether "off-line" or "on-line" coupling is more suitable.

The ever recurring dream of users of modern liquid chromatography—that someone will invent a relatively simple, reliable detector that is *not substance specific*—will not be discussed here.

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Appendix

As shown previously, the basic empirical equations are:

$$\delta = \sqrt{10^3 K_1} = \sqrt{\frac{10^3 \varepsilon_1 \eta u L}{\Delta P}} \tag{2}$$

$$h = a\delta + \frac{b}{u} + c\delta^2 u \tag{4}$$

Where a, b, c, ε_1, and η must be treated as system-dependent constants. The intensive quantities h and u are substituted by the extensive quantities (L/n and L/t_0) so that five variables appear: n, L, t_0, ΔP, and δ. With the definitions

$$n = L/h \tag{A1}$$

$$u = L/t_0 \tag{7}$$

the two following equations result

$$L = \delta \sqrt{\frac{t_0 \Delta P}{10^3 \eta \varepsilon_1}} \tag{8}$$

$$n = \frac{L}{a\delta + \frac{b t_0}{L} + \frac{c\delta^2 L}{t_0}} \tag{A2}$$

The independent variable L can be eliminated:

$$n = \left[\frac{a\sqrt{10^3 \eta \varepsilon_1}}{\sqrt{t_0 \Delta P}} + \frac{10^3 b \eta \varepsilon_1}{\delta^2 \Delta P} + \frac{c\delta^2}{t_0}\right]^{-1} \tag{9}$$

The maximum in the n,δ-curve follows by differentiation:

$$\left(\frac{\partial n}{\partial \delta}\right)_{t_0, \Delta P} = 0 \tag{A3}$$

$$\left(\frac{\partial n}{\partial \delta}\right)_{t_0, \Delta P} = \frac{\frac{2c\delta}{t_0} - \frac{2 \times 10^3 b \eta \varepsilon_1}{\delta^3 \Delta P}}{([\text{eq. } 9])^2} \tag{A4}$$

As long as eq. (9) $\neq 0$, which always applies in chromatographic systems, then for the maximum

$$\frac{2c\delta}{t_0} - \frac{2 \times 10^3 b \eta \varepsilon_1}{\delta^3 \Delta P} = 0 \tag{A5}$$

with the physically meaningful solution:

$$\delta_{opt} = \left[\frac{10^3 b \eta \varepsilon_1}{c} \cdot \frac{t_0}{\Delta P}\right]^{1/4} \tag{A6}$$

Since a further degree of freedom is lost at the maximum the following equations with two variables result:

$$L_{opt} = \left(\frac{b}{10^3 c \eta \varepsilon_1} \Delta P t_0^3\right)^{1/4} \tag{A7}$$

$$\eta_{opt} = \frac{1}{a + 2\sqrt{bc}} \sqrt{\frac{\Delta P t_0}{10^3 \eta \varepsilon_1}} \tag{A8}$$

From eq. (A7) and eq. (7) it follows that the linear velocity at the maximum of the n,δ-curve is

$$u_{opt} = \left(\frac{b}{10^3 c \eta \varepsilon_1} \cdot \frac{\Delta P}{t_0}\right)^{1/4} \tag{A9}$$

If eq. (A6) is solved for $\Delta P/t_0$ and substituted into eq. (A9) it follows that:

$$u_{opt} = \frac{1}{\delta} \cdot \sqrt{\frac{b}{c}} = u_{min} \tag{10}$$

as discussed in Section 3.

The equation for the $n/t_0,\delta$-curve in Figures 4 and 5 results when eq. (9) is solved with respect to t_0:

$$\sqrt{t_0} = -\frac{e}{2f} \pm \sqrt{\left(\frac{e}{2f}\right)^2 - \frac{g}{f}} \tag{A10}$$

with

$$e = an\sqrt{\frac{10^3 \eta \varepsilon_1}{\Delta P}} \tag{A11}$$

$$f = \frac{10^3 bn \eta \varepsilon_1}{\delta^2 \Delta P} - 1 \tag{A12}$$

$$g = cn\delta^2 \tag{A13}$$

Of the two solutions to eq. (A 10) only the positive one is physically meaningful. This solution possesses two branches with a discontinuity at

$$\delta_{disc} = \sqrt{\frac{10^3 b n \eta \varepsilon_t}{\Delta P}} \tag{A 14}$$

The branch where $\delta \leq \delta_{disc}$ has no physical meaning.

Instead of representing t_0 as a function of n, ΔP, and δ using eq. (10), the reciprocal of this equation can be calculated and multiplied by n, so that the speed of analysis n/t_0 is obtained as a function of n, ΔP, and δ:

$$\frac{n}{t_0} = n\left[\frac{1}{2}\left(\frac{e}{f}\right) - \frac{e}{f}\sqrt{\left(\frac{e}{2f}\right)^2 - \frac{g}{f}} - \frac{g}{f}\right] \tag{A 15}$$

In order to calculate the nomogram, eqs. (A 6), (A 7), and (A 8) successively, were transformed so that n_{opt} was a function of δ_{opt} and one other parameter (either ΔP_{opt}, L_{opt} or $t_{0,opt}$):

$$n_{opt} = \frac{\sqrt{c/b}}{10^3 \eta \varepsilon_t (a + 2\sqrt{bc})} \cdot \delta_{opt}^2 \Delta P_{opt} \tag{A 16}$$

$$n_{opt} = \frac{1}{a + 2\sqrt{bc}} \cdot \frac{L_{opt}}{\delta_{opt}} \tag{A 17}$$

$$n_{opt} = \frac{\sqrt{b/c}}{a + 2\sqrt{bc}} \cdot \frac{t_{0,opt}}{\delta_{opt}^2} \tag{A 18}$$

List of Symbols:

a, b, c	Constants in eq. (4)
As	Asymmetry factor (23)
D_m	Diffusion coefficient of the sample in the eluent
F	Flow velocity
$h = L/n$	Height equivalent to a theoretical plate
h_{min}	h at the minimum in the h,u curve
K_t	Permeability defined in terms of the empty column velocity [eq. (2)]
$k' = (t_R - t_0)/t_0 = t'_R/t_0$	Capacity factor
L	Column length
n	Number of theoretical plates
n/t	Speed of analysis (plates per unit time)
ΔP	Pressure drop in a column
$R = (t_{R2} - t_{R1})/w$	Resolution
r	Internal radius of a column
t_0	Elution time of an inert sample
t_R	Elution time of a retarded sample
u	Linear velocity of the eluent
u_{min}	u at the minimum of the h,u curve
V_t	Column empty volume
V_m	Volume of eluent in the column
w	Intercept on the time axis of the tangent of the inflexion
$\alpha = k'_2/k'_1$	Relative retention
δ	Chromatographically defined particle size [eq. (2)]
ε_t	Total porosity
η	Viscosity of the eluent

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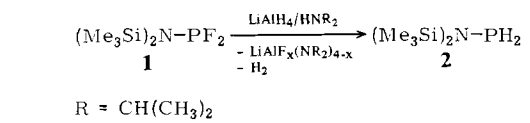
Bis(trimethylsilyl)aminophosphane**

By *Edgar Niecke** and *Reinhold Rüger*

The stability[1] and synthetic potential[2] of the secondary aminophosphane *N,N,N'*-tris(trimethylsilyl)diaminophosphane stimulated our investigations into the synthesis of a primary aminophosphane.

We have now obtained bis(trimethylsilyl)aminophosphane **2** as the first representative of this class of compounds by selective F/H exchange in bis(trimethylsilyl)aminodifluorophosphane **1**[3] with $LiAlH_4/HN(iPr)_2$.



2 is a water-clear, highly pyrophoric liquid, which is stable up to at least 100 °C. Its composition is confirmed by elemental analysis and by its mass spectrum [70 eV: *m/z* 193 (M^+, 30%), 192 ($M^+ - H$, 2.3), 191 ($M^+ - H_2$, 1.5), 178 ($M^+ - Me$, 100) *etc.* The $H_2P—NSi_2$ skeletal framework can be deduced from the following characteristic IR absorptions of gaseous **2**: 2260 m, 2255 sh $\nu_{as,s}(PH_2)$, 1070 m $\delta(PH_2)$, 981 m $\nu(PN)$, 903 s $\nu_{as}(NSi_2)$, and 479 cm^{-1} m $\nu_s(NSi_2)$.

The triplet structure of the signal at $\delta = -59.3$ ($^1J_{HP} = 189.4$ Hz) in the ^{31}P-NMR (30% in CD_2Cl_2, H_3PO_4 ext.) proves the presence of a PH_2-group; the amine ligand leads to a stronger deshielding of the phosphorus nucleus than in primary phosphanes[4]. The ^1H-, $^{13}C\{^1H\}$- and $^{29}Si\{^1H\}$-NMR spectra (30% in CD_2Cl_2, TMS int.) show the signal to be expected for free rotation about the P—N bond: ^1H: $\delta = 0.29$ ($^4J_{HP} = 1.1$ Hz), 4.75 ($^1J_{HP} = 189.5$ Hz); ^{13}C: $\delta = 1.14$ ($^3J_{CP} = 5.3$ Hz), and ^{29}Si: $\delta = 10.41$ ($^2J_{SiP} = 10.8$ Hz).

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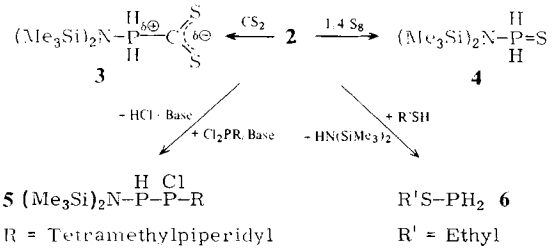
The high reactivity towards oxidative attack, *e.g.* nucleophilic substitution at the phosphorus atom makes **2** an extremely interesting synthon. For example, **2** smoothly reacts with carbon disulfide or sulfur with increase in coordination number of the phosphorus to give **3**[5] and **4**[5], respectively, while reaction with dichlorophosphanes affords access to β-functional diphosphanes such as **5**[5] and with thiols yields mercaptophosphanes such as **6**[5].



Experimental

All experiments were carried out under an inert gas with rigorous exclusion of air and moisture. The solvents were re-purified and dried by column chromatography on Al_2O_3 (super I, basic).—**2**: $LiAlH_4$ (1.14 g, 30 mmol) and $HN(iPr)_2$ (2.2 g, 20 mmol) are added to a solution of **1** (6.97 g, 30 mmol) in pentane (60 mL) at −20 °C. The mixture is stirred and treated with 10 mL of THF, which initiates reaction (evolution of gas). Stirring is continued for a further 24 h, during which time the mixture is allowed to warm to room temperature. Solvent and product are collected under oil-pump vacuum in three cold traps (−10, −50, −196 °C), whereby the residue is heated to 50 °C. **2** condenses at −10 and −50 °C together with solvent residues. Fractional distillation under vacuum furnishes 3.15 g (16 mmol ≙ 53%) of pure **2**.

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[5] ^{31}P-NMR: **3**: $\delta = 2.4$ (t, $^1J_{HP} = 496$ Hz); **4**: $\delta = -0.4$ (t, $^1J_{HP} = 490$ Hz); **5** (preferred stereoisomer): $\delta = 61.1$ (d, d, $^1J_{PP} = 151$ Hz, $^2J_{HP} = 35$ Hz); 6.0 (d, d, $^1J_{PP} = 151$ Hz, $^1J_{HP} = 201.5$ Hz); **6**: $\delta = -115$ (tt, $^1J_{HP} = 193$ Hz, $^3J_{HP} = 7.3$ Hz).

Palladacycloalkanes by Oxidative Coupling of 3,3-Dimethylcyclopropene with Palladium(0) Compounds**

By *Paul Binger**, *Holger Michael Büch*, *Reinhard Benn*, and *Richard Mynott*

Transition metal-catalyzed cyclooligomerization of alkenes proceeds smoothly and in high yields if the double

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[**] Metallacycloalkanes, Part 4. This work forms a part of a thesis by H. M. Büch, Universität Kaiserslautern, planned for 1982.—Part 3: [1].

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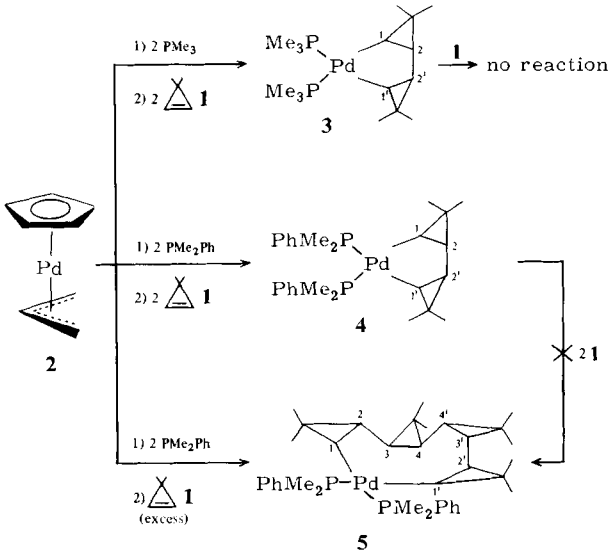
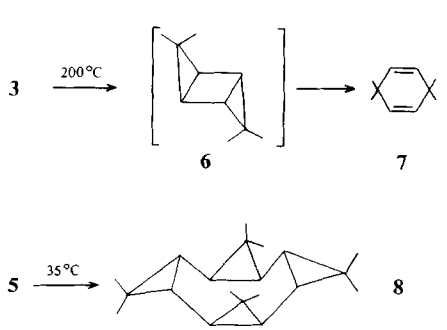
bond of the substrate is activated by ring strain. Thus, *e.g.*, 3,3-dimethylcyclopropene **1** is cyclooligomerized, sometimes highly chemoselectively, on palladium(0) catalysts[2]. Palladacycloalkanes of various ring size have been discussed as intermediates.

We have now succeeded in preparing five- and nine-membered palladacycloalkanes in stoichiometric reactions, and have simulated a catalytic cycle by their thermal decomposition. We synthesized the colorless palladacycloalkanes **3** to **5** by reaction of the dark-red complex (η^3-allyl)(η^5-cyclopentadienyl)palladium **2** with the relevant phosphane and **1** at -30 to $+20$ °C in hexane. To our knowledge **3** to **5** are the first palladacycloalkanes to have been obtained by oxidative coupling of alkenes. In contrast, diligand palladacyclopentanes are readily accessible by elimination of LiCl[3].



With trimethylphosphane as ligand, only the metallacyclopentane derivative **3** is obtained. With dimethylphenylphosphane, the five-membered ring **4**, the nine-membered ring **5**, or (with **2**:**1** = 1:3) a mixture of equal parts of **4** and **5** are formed depending on the ratio **2**:**1**. A palladacycloheptane derivative could not be isolated. Neither **3** nor **4** undergo further reaction with **1**. **4** and **5** are apparently formed from the same precursor—possibly a dinuclear complex.

Under inert gas, **3** and **4** first start to decompose at *ca.* 170–175 °C; **5** already decomposes at *ca.* 85 °C. In solution (decalin), the hydrocarbon residue is completely cleaved from **3** within 4 h on heating to 200 °C; in the case of **5**, reductive elimination can be achieved even in boiling diethyl ether. The products of thermolysis are the cyclohexadiene derivative **7** and the cyclotetramer **8**, respectively[2, 7]. The precursor for formation of **7** must be the tricyclohexane **6**, which rearranges quantitatively to **7** under the reaction conditions.



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German version: *Angew. Chem.* **94** (1982) 66
Angew. Chem. Suppl. **1982**, 153

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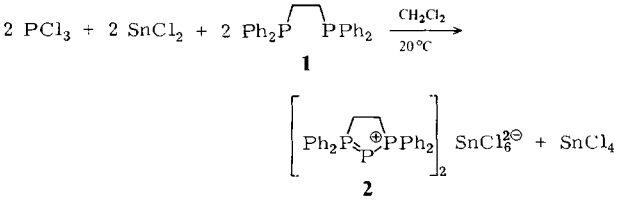
A diphos-Complex of $P^{\oplus}$: The 1,1,3,3-Tetraphenyl-1λ^5,2λ^3,3λ^5-triphospholenyl Cation**

By *Alfred Schmidpeter**, *Siegfried Lochschmidt*, and *William S. Sheldrick**

Dedicated to Professor Oskar Glemser on the occasion of his 70th birthday

In reactions which should lead to phosphorus(I) halides PX (X = Cl, Br, I), such as the reduction of phosphorus(III) halides PX_3[1a], the disproportionation of diphosphorus tetrahalides P_2X_4[1b], or the decomposition of dihalophosphanylmetal compounds L_nMPX_2[1c], orange-red, X-ray-amorphous solids, some with X/P ratios widely differing from 1, are formed.

The product obtained on reaction of PCl_3 with $SnCl_2$ in the presence of [18]crown-6/KCl in dichloromethane also separates, quantitatively, as an orange-red precipitate. However, if the reaction is carried out in the presence of ethylenebis(diphenylphosphane) **1** (diphos) a clear solution is formed, from which the hexachlorostannate of the title cation **2** can be isolated as well-formed, colorless crystals (m.p. 230 °C).



The "complex cation" in **2** is the first phosphorus(I) compound in which the formal charge of $P^{\oplus}$ is also preserved as a net charge. It thus completes the series L_2P^n, $n = -1$ (two anionic ligands L, *e.g.* NC—P—CN[2a], $(RO)_2OP$—P—$PO(OR)_2$[2c]), $n = 0$ (one anionic, one neutral ligand, *e.g.* R_3P—P—CN[2b], R_3P—P—$PO(OR)_2$[2d] with $n = +1$ (two neutral ligands). On the other hand, **2** can be regarded as an unusual 1,2,3-triphospholane derivative[3].

The structure of the cation follows from its ^{31}P-NMR spectrum: AB_2 type, $\delta_{P(A)} = -231.6$, $\delta_{P(B)} = +63.8$,

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[**] Four- and Five-Membered Phosphorus Heterocycles, Part 54. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 53: A. Schmidpeter, K. Karaghiosoff, *Z. Naturforsch. B* **36** (1981) 1273.

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J_{PP} = 448.9 Hz. The chemical shift of the central phosphorus $\delta_{P(A)}$ continues the trend found for the other L_2P'' compounds mentioned above (δ_P = −188 to −218), as $^1J_{PP}$ corresponds to the coupling constants found in those compounds.

According to an X-ray structure analysis, **2** crystallizes with two molecules of CH_2Cl_2. The five-membered ring of the cation (Fig. 1) has an envelope conformation. While in most other cases the PP bond length is "remarkably constant at 220–225 pm and seems insensitive to the bonding situation at the phosphorus"[4], here it is considerably shorter. The angle at the central phosphorus is very small, but is also just as small at the doubly coordinated phosphorus in diazaphospholene[5].

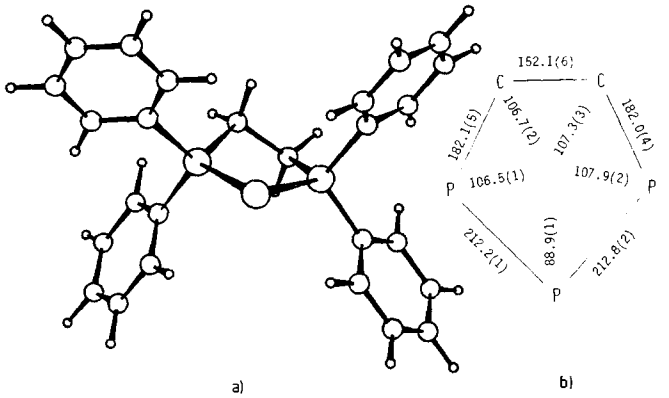

Fig. 1. a) Structure of the cation in $2 \cdot 2CH_2Cl_2$; monoclinic, space group $P\bar{1}$, a = 1165.5(2), b = 1317.4(3), c = 1098.2(6) pm, α = 100.38(2), β = 98.55(3), γ = 68.20(20)°, Z = 2, ρ_{calc} = 1.47 g/cm^{-3}, 4091 independent reflections ($Mo_{K\alpha}$, $F^2 \geq 2.0\sigma(F^2)$, $2\theta \leq 50°$), R = 0.042, R_w = 0.040.—b) Bond lengths [ppm] and angles [°] in the triphospholane ring.

Further experiments show that the "complexes" $L_2P^{\oplus}$ are variable, both with respect to the phosphane ligands L, and as regards the generation of $P^{\oplus}$; in particular, acyclic species can also be prepared.

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Is Hexazine Stable?

By *Hanspeter Huber**

Dedicated to Professor Edgar Heilbronner on the occasion of his 60th birthday

Vogler et al.[1], on the basis of experimental evidence, have recently postulated that N_6 (hexazine, hexaazobenzene, cyclohexaazatriene) exists at low temperatures. In the discussion of evidence, three theoretical papers were cited, one of which[2b] was effectively interpreted as indicating that N_6 "is slightly stabilized". A considerably more accurate calculation is presented in the following; earlier work is shown in a critical light.

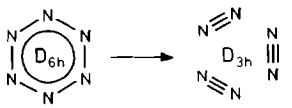
The semiempirical studies of *Dewar*[2c] involve two calculations: A MINDO/3 calculation predicts that hexaazine is more stable than dinitrogen; this result is considered to be unreliable by *Dewar*, because repulsion between the lone pairs of electrons is not considered. A MNDDO/1 calculation indicates that N_6 is approximately 1351 kJ/mol higher in energy than $3N_2$, and decomposes without an activation barrier.

In their *ab initio* SCF calculation, without geometrical optimization, *Palmer et al.*[2a] used a minimal basis. The energies thus obtained are shown in Table 1. No statement was made about the stability of hexazine.

Table 1. Theoretical comparison of stabilities of hexazine/dinitrogen.

Method	N_6, E/E_h	N_2, E/E_h	$(N_6 - 3N_2)$, E/kJ mol
Ref. [2a]	−325.290	−108.526	756
Ref. [2b]	−325.468	−108.569	631
FOGO	−325.988	−108.801	1089

Wright[2b] also used a minimal basis in his *ab initio* SCF calculations with geometrical optimization under D_{6h} symmetry. The energies for the optimal bond lengths of 137.9 pm are also included in Table 1. By comparison with standard bond energies, and the corresponding calculation for N_4, he comes to the conclusion that hexazine exhibits "a genuine stabilizing effect". However, whether the decomposition $N_6 \rightarrow 3N_2$ is hindered by an activation barrier was not investigated. Such a decomposition would only be possible if the symmetry were lowered from D_{6h} to D_{3h}.



Starting from *Wright*'s geometry[2b] we optimized the structure of N_6 with D_{6h} symmetry. We used the FOGO method[3] with sliding orbitals; this corresponds to a (DZ + P) basis and is, hence, a considerable improvement on the earlier calculations with minimal bases (the total energy lies approximately 1360 kJ/mol lower than that of the previous best calculation[2b]). The energy for an NN separation of 131.1 pm, which is found for the stationary point, is also reproduced in Table 1.

In order to decide whether this stationary point is a genuine minimum, the force constant matrix was calculated using *Pulay*'s "force" method[4]. Normal coordinate analysis indicated that this is *not a minimum, but, rather, a saddle point*. From the results of our calculations, N_6 with D_{6h} symmetry is not stable, but decomposes without an activation barrier in accord with *Dewar*'s MNDDO/1 calculation. Based on experience with calculations of this level, the result should not differ substantially by extending the basis. A geometrical optimization including electron correlation (and a sufficiently large basis) is too involved at present. The influence of the electron correlation on the stability is difficult to estimate. Also, stabilization by solvation cannot be completely excluded.

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In summary, none of the calculations yield an activation energy and (with the exception of the MINDO/3 calculation) all predict that in the gas phase N_6 is *ca.* 10^3 kJ/mol less stable than $3N_2$. For as long as no direct experimental proof for the existence of N_6 exists we must assume that hexazine is neither thermodynamically nor kinetically stable.

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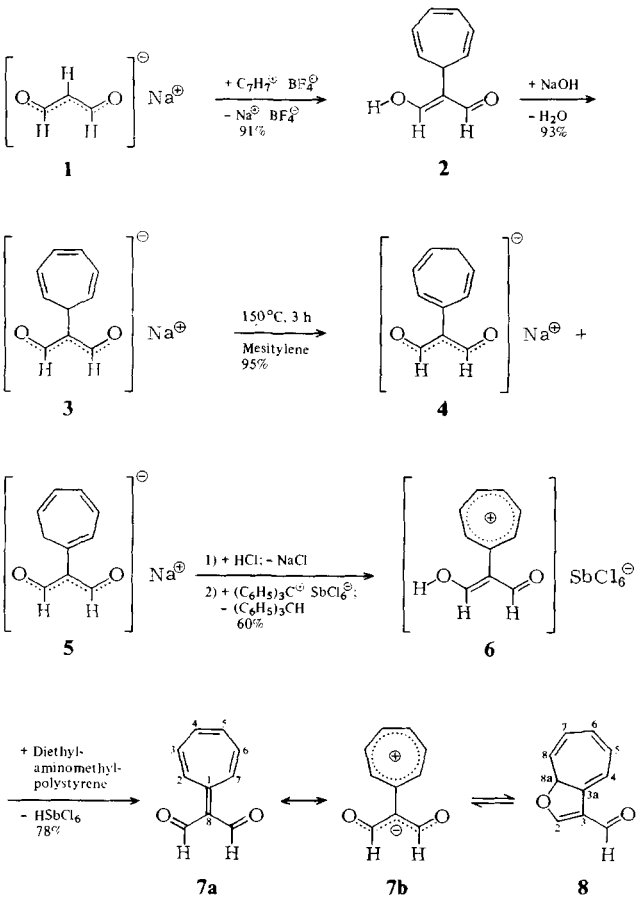
2,4,6-Cycloheptatrienylidenemalondialdehyde (8,8-Diformylheptafulvene)**

By *Christian Reichardt** and *Kyeong-Yeol Yun*

Since they cannot be enolized, 2,2-substituted malondialdehydes[1] and alkylidenemalondialdehydes[5] are real C_3 dialdehydes and therefore valuable C_3-synthetic building blocks.



Scheme 1.

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[**] Syntheses with Aliphatic Dialdehydes, Part 30. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. — Part 29: [1].

We report here on the preparation of the title compound **7**, which belongs to the hitherto rarely investigated cycloalkylidenemalondialdehydes. Starting from the sodium salt **1** of malondialdehyde, **7**[10] is obtainable as orange-red crystals (m.p. 132—133 °C, dec.) *via* the isolable intermediates **2** to **6** (Scheme 1).

According to NMR spectra, **7** is in equilibrium with the valence isomer 3-formyl-8a*H*-cyclohepta[b]furan **8** in solution (D_2O: 100% **7**; CCl_4: 37% **7**).

The X-ray structure analysis shows that exclusively the valence isomer **7** exists in the crystal. As a result of steric interactions, between 2-H/7-H on the one hand, and the two aldehyde oxygen atoms on the other, the seven-membered ring and the malondialdehyde group are rotated through 18.1° with respect to each other. This and the participation of the dipolar mesomeric resonance structure **7b** lead to a relatively long C-1/C-8 bond (143 pm; C_{sp^2}—C_{sp^2} single bond: 148 pm; double bond: 134 pm).

MNDO calculations[16] give a dipole moment of 3.0 D for a partially optimized completely planar conformation of **7**. An experimental determination of the dipole moment of **7** was not possible owing to the concomitant presence of the valence isomer **8** in solution.

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Angew. Chem. Suppl. 1982, 113

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[10] The constitution of **7** follows from the elemental analysis, the ^1H- and ^{13}C-NMR spectra, as well as an X-ray structure analysis. We thank Dr. W. Massa and R. Schmidt, Fachbereich Chemie, Universität Marburg, for carrying out the X-ray structure analysis.
[16] M. J. S. Dewar, W. Thiel, *J. Am. Chem. Soc. 99* (1977) 4899; we thank Dr. E.-U. Würthwein, Universität Erlangen-Nürnberg, for the MNDO calculations.

Convenient General Synthesis of Alkynylcyclopropanes**

By *Thomas Liese* and *Armin de Meijere**

Dedicated to Professor Oskar Glemser on the occasion of his 70th birthday

Although donor-, acceptor-, as well as vinyl-substituted cyclopropanes have become established synthetic tools, alkynylcyclopropanes[4], which because of the junction of a cyclopropyl and an alkynyl group offer an interesting and powerful synthetic potential, have not been widely recognized.

We recently found that the easily accessible 1-chloro-1-(trichlorovinyl)cyclopropanes **1**[5] react cleanly with 2 moles of *n*-butyllithium to give (1-chlorocyclopropyl)-substituted lithium acetylides **6** (Scheme 1), which can be solvolyzed by methanol or water to yield (1-chlorocyclopropyl)acetylenes **7** (Table 1) or trapped by a wide variety of electrophiles EX to give acetylene derivatives **5a** (Table 2).

The 1-chloro-1-alkynylcyclopropanes **5** and **7** are polyfunctional molecules, and as such valuable building blocks for organic synthesis. Among the reactions which can be

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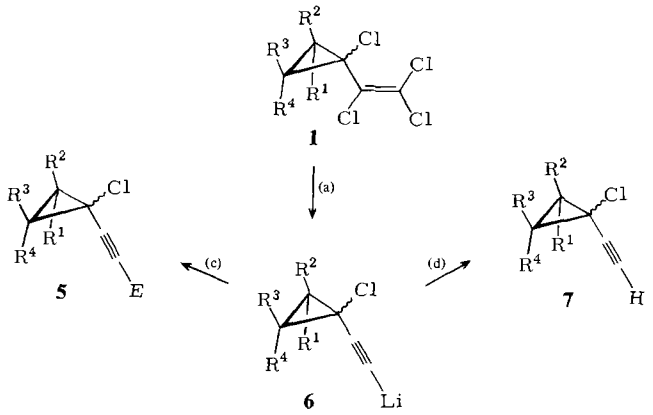

Scheme 1. (a) 2 mol *n*BuLi/mol **1**, Et_2O/*n*-hexane, −78 °C; (b) MeOH, THF, −78 °C; (c) EX, −20 to 0 °C, 1–4 h; (d) MeOH, RT.

Table 1. (1-Chlorocyclopropyl)acetylenes **7** from **1**.

	R^1	R^2	R^3	R^4	Yield [%] [b]
a	CH_3	CH_3	CH_3	CH_3	82 (A)
b [a]	CH_3	CH_3	CH_3	H	80 (B)
c	CH_3	CH_3	H	H	76 (A)
d	H	CH_3	H	CH_3	82 (B)
e [a]	*n*-C_3H_7	H	H	H	91 (B)
f [a]	H	—$(CH_2)_4$—		H	81 (B)

[a] Mixture of stereoisomers. [b] Isolation: A: Short-path distillation, B: Preparative gas chromatography.

Table 2. (1-Chloro-2,2,3,3-tetramethylcyclopropyl)acetylene derivates **5a** from **1a**.

EX	[mol] [a]	E	M.p. [°C]	Yield [%] [b]
CO_2	— [c]	COOH	159–161	91 (A)
$ClCO_2Me$	5	COOMe	—	85 (B)
Me_3SiCl	1.1	$SiMe_3$	68	74 (A, C)
$(CH_3O)_2SO_2$	2.5	CH_3	43	68 (D)
CH_3COCH_3	1.1	$C(OH)(CH_3)_2$	58.5	83 (C, D)
$(CH_2)_5C{=}O$	1.1	$C(OH)(CH_2)_5$	102	85 (C)
$(H_2CO)_n$	4	CH_2OH	55	67 (C, D)
n-BuBr [c]	10 [d]	*n*Bu	—	76 (D)
NCS	8	Cl	38	70 (B)
CH_3SSCH_3	6.5	SCH_3	39.5	63 (D)
$(CH_3CO)_2O$	10	$COCH_3$		54 (C)

[a] mol EX/mol **1a**. [b] Isolation A: recrystallisation, B: distillation, C: sublimation, D: column chromatography. [c] Gaseous CO_2 introduced. [d] Addition of 30 mol% hexamethylphosphoric triamide necessary. [e] *N*-Chlorosuccinimide.

performed with them are the exchange of chlorine with other substituents (*via* lithiation of **5** (E = $SiMe_3$) and consecutive electrophilic substitution), ring opening to enines (with Lewis acids), transformation to cyclopropyl ketones (by mercuric salt catalyzed hydration) and to cyclopropane carboxylic acids (by ozonization).

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German version: *Angew. Chem.* 94 (1982) 65
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Thermal Conversion of 1,3-Cyclooctadien-5-yne into Benzocyclobutene—A Novel Isomerization on the C_8H_8 Hypersurface**

By *Herbert Meier**, *Norbert Hanold*, and *Heinz Kolshorn*

Synthesis of the first highly-strained cyclic enyne was accomplished some time ago[3]. Incorporation of a double bond into the cyclooctyne ring system considerably increases the geometric strain; insertion of two double bonds is expected to lead to a still greater increase in strain. Figure 1 shows the enthalpies of formation of 1,3,5-cyclooctatriene and 1,3-cyclooctadien-5-yne calculated on the basis of complete optimization of geometry according to the MNDO method[4]. Both molecules have a C_1 conformation in the lowest energy state. *cis*-2-Butene (with C_{2v} symmetry) and 2-butyne (with D_{3d} symmetry) are listed as reference systems. A characteristic feature is the large difference in the heat of hydrogenation in the *cyclo*-C_8- and C_4-systems (236 and 120 kJ/mol, respectively). The high value for the hydrogenation of cyclooctadienyne to cyclooctatriene is ascribed to release of ring strain. The difference in the heat of hydrogenation of the two systems (116 kJ/mol) can be regarded as a direct measure of the geometrical ring strain[3].

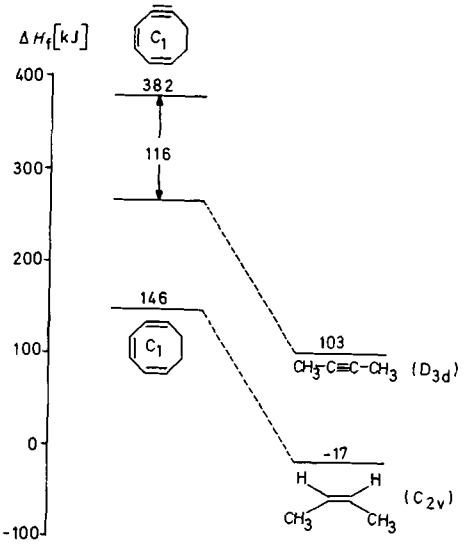

Fig. 1. Comparison of the heats of hydrogenation of 1,3-cyclooctadien-5-yne and 2-butyne on the basis of calculated[4] enthalpies of formation ΔH_f.

1,3-Cyclooctadien-5-yne **7** was obtained by thermal fragmentation of the selenadiazole compound **6**. **7** can be converted into **8**, *e.g.*, by reaction with tetracyclone. On attempting to condense **7** directly into a cold trap, only traces of the compound remained unchanged; to our surprise we isolated almost exclusively benzocyclobutene **10**. Apparently **7** is far much less stable than the isomeric 1,5-cyclooctadien-3-yne[11].

The conversion must take place on the S_0 energy hypersurface of the C_8H_8 hydrocarbon with a relatively low activation barrier. This behavior is reminiscent of the valence

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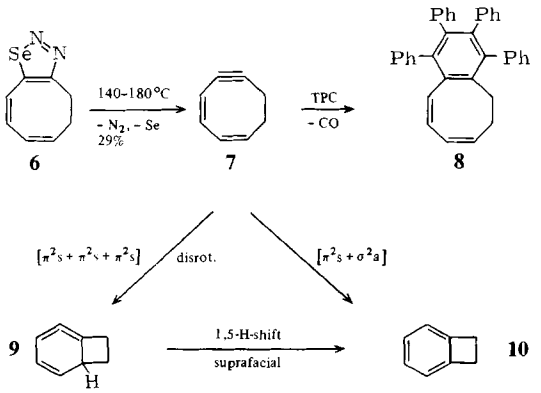
tautomerism 1,3,5-cyclooctatriene ⇌ bicyclo[4.2.0]octa-2,4-diene[12], but the bicycle **9** corresponding to **7** is energetically very unfavorable. As an alternative, we suggest addition of the C1—H bond as antarafacial 2σ component to the triple bond as suprafacial 2π component.



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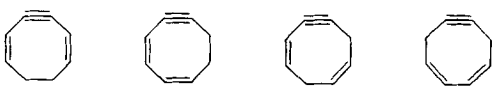
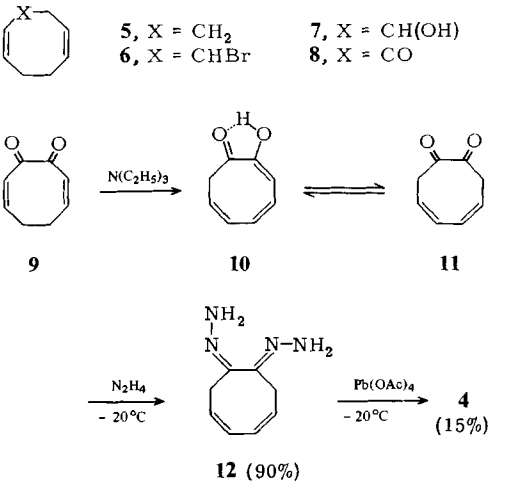
1,3-Cyclooctadien-6-yne—An Isolable Bishomodehydrobenzene**

By *Herbert Meier** and *Toni Echter*

The highly strained and highly reactive cyclooctadienynes belong to the C_8H_8-series of hydrocarbons. Of the four constitutional isomers **1**—**4**, only the 1,5-cyclooctadien-3-yne **1** has so far been isolated[1] (half-life of a 0.3 M solution in chloroform *ca.* 2 h). According to a MNDO calculation there is very little difference in the standard enthalpies of formation of **1**—**4** ($\Delta\Delta H_f < 2$ kcal/mol)[2]. Aside from oligomerizations, isomerizations on the C_8H_8 S_0-energy hypersurface are particularly decisive regarding kinetic stability. Thus, on attempted isolation **2** and **3** are converted into benzylcyclobutene and styrene.

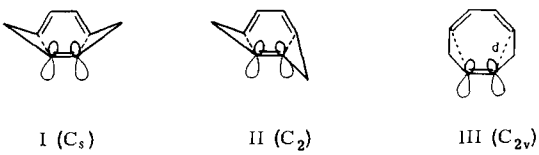


We have now synthesized 1,3-cyclooctadien-6-yne **4** from 1,5-cyclooctadiene **5** *via* the intermediates **6**—**8**[1], **9**[3], **10**[3], **11**, and **12**. Compound **4**, a colorless oil which solidifies at *ca.* −20 °C, can function as diene as well as dienophile in Diels-Alder reactions.



4 (as oil) has a half-life of *ca.* 5 h at room temperature; when dissolved in chloroform it is stable for a number of days.

Is **4** a bishomodehydrobenzene with a stabilizing π-electron sextet? Such a species could have the conformations I—III, in each of which the diene moiety and the triple bond are coplanar. The MNDO calculation gives a lowest energy C_2 conformation, which deviates only minimally



from the planar C_{2v} conformation[2]. The four methylene protons are chemically equivalent. This would imply conformation III or that of I/II with rapid ring inversion (on the NMR time-scale). The ^{1}H-NMR spectrum also remains practically unchanged on cooling. An almost planar C_2-form should in fact have a very low inversion barrier. The distances *d* (dotted) between the diene moiety and the triple bond are of decisive importance for the π-electron sextet theory. According to the MNDO calculation and the spectroscopic characterization, all data indicate that **4** is planar or almost planar and that *d* has a relatively large value. Hence, the homoaromaticity is, any case, subordinate to the geometric strain[5], *i.e.* a higher deformation energy cannot be compensated or even over-compensated by better overlapping in the π-electron sextet. Thus, there are no thermodynamic reasons for the greater stability of **4** compared to that of **1**—**3**; rather it is of a kinetic nature.

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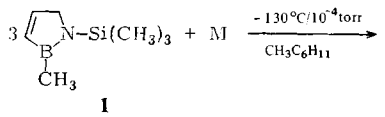
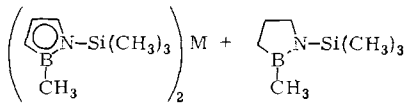
Azaborolinyl-Iron and -Cobalt Sandwich Complexes by Metal Atom Synthesis**

By *Saeid Amirkhalili, Uwe Höhner,* and *Günter Schmid**

Anions of 1,2-azaborolines, which are isoelectronic with cyclopentadiene, could be used as 6 π electron donors in numerous carbonyliron complexes[1-4]; until now, sandwich compounds have been inaccessible. We have now prepared, for the first time, the ferrocene and cobaltocene analogues **2** and **3**, respectively, by metal atom synthesis from **1**[3].



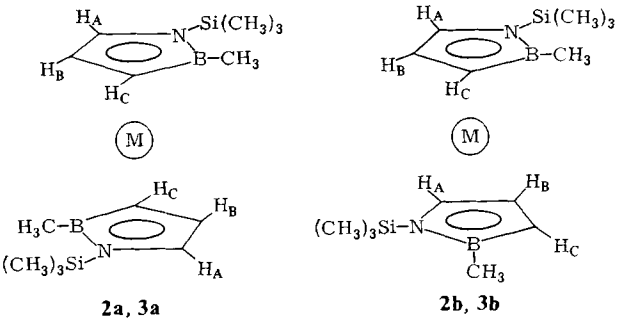
1



2, M = Fe
3, M = Co

4

The red-brown, diamagnetic **2** and the green, paramagnetic **3** can each be separated by fractional sublimation *in vacuo* into isomers, which can be characterized as the staggered form **a** and eclipsed form **b** by X-ray structural analysis.



2a, 3a **2b, 3b**

In the mass spectra of **2** and **3**, the molecular ions appear at $m/z = 360$ (100%) and 363 (100%), respectively. The ring protons H_A, H_B, and H_C of **2a** and **2b** show separate signals in the ^{1}H-NMR. The ^{11}B-NMR signals of **2** ($\delta = 24 \pm 1$) and **3** ($\delta = 22 \pm 1$) are, as expected, shifted upfield relative to the signal of **1** ($\delta = 38$). From the crystal structure analysis, the *pentahapto*-bound heterorings are planar; this result, and the ^{11}B-NMR spectra document the involvement of the boron atoms in the interaction of the rings with the metal atoms.

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[**] Azaborolinyl-Metal Complexes, Part 5. This work was supported by the Landesamt für Forschung in Nordrhein-Westfalen and by the Fonds der Chemischen Industrie. – Part 1–4: [1–4].

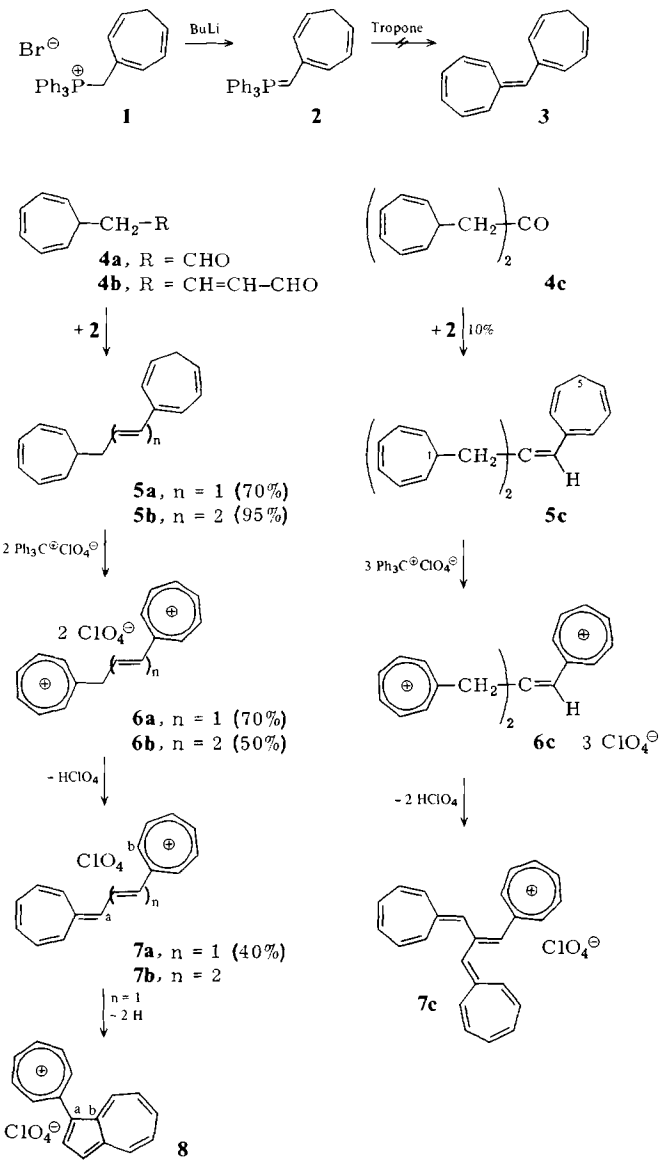
Polymethines with Heptafulvenyl Terminal Groups**

By *Norbert Ott* and *Dieter Rewicki**

Dedicated to Professor Georg Manecke on the occasion of his 65th birthday

Numerous carbanionomethines with anion-stabilizing carbocyclic terminal groups have been described as conjugated bases of "highly acidic" hydrocarbons[1]. The corresponding cationic polymethines on the other hand, are hardly known[2].

The key compound of our synthesis is deep-red **2** (generated from **1**[3] by reaction with *n*-butyllithium in tetrahydrofuran[4]), which reacts smoothly with aldehydes and ketones to give 1,3,6-cycloheptatrienylalkenes. **2** reacts quantitatively with tropone even at −50 to 25 °C; however, we could not isolate either the thermolabile **3** or **7**, $n = 0$[2b]. It should be possible, on the other hand, to synthesize the cationic polymethines **7a**–**7c** from the carbonyl compounds



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4a—**4c** without formation of neutral heptafulvene intermediates.

In CH_3CN/H_2O (95:5), the crystalline dication salt **6a** [$\lambda_{max}=348$ nm ($\log\varepsilon=4.20$), in CF_3CO_2H/H_2SO_4] obtained from **4a** furnishes the deep blue trimethine **7a** in quantitative yield. Chromatography (CH_3CN/CH_2Cl_2 1:1) on deactivated silica gel affords **7a** [dark blue crystals, decomp. >250 °C; $\lambda_{max}=713$ nm ($\lg\varepsilon=4.88$), in CH_3CN; ^{1}H-NMR (CD_3CN): $\delta=6.48$ (2H, d, $J=13.2$ Hz), 7.2—7.8 (m, 12H), 8.26 (1H, t, $J=13.2$ Hz); pK_{R^+} (in CH_3CN/H_2O (1:1))=6.90; for comparison: tropylium perchlorate: $pK_{R^+}=4.01$]. **7a** cyclizes in solution to give a violet carbocation [λ_{max} ($\lg\varepsilon$)=554 nm (4.38), in CH_3CN], which was isolated as the crystalline perchlorate **8**[5]. The previously[6] described synthesis of **7a** leads to other products.

6b was obtained analogously to **6a**; in CH_3CN/H_2O it forms olive-green non-isolable **7b** [$\lambda_{max}=817$ nm ($\lg\varepsilon>4.5$), $pK_{R^+}=4.9$]. In trifluoroacetic acid, **7a** and **7b** are quantitatively converted into **6a** and **6b**, respectively.

Attempted synthesis of **7c** failed at the step **5c** (from **4c**)→**6c** [**5c**: oil, MS: m/z 326 (M^+), ^{1}H-NMR: $\delta=1.77$ (m, 2H-1) and 2.26 (t, 2H-5)]. Since hydride abstraction from C7-substituted cycloheptatrienes is difficult, **5c** was heated for 30 min at 200 °C; an isomeric mixture with almost double the amount of C3-substituted seven-membered rings (*i.e.* 1,3,6-cycloheptatrienyl groups) was formed. After hydride transfer with trityl perchlorate in dichloromethane, treatment with ether leads to precipitation of a mixture of perchlorates, which dissolve in CH_3CN/H_2O to give a blue solution ($\lambda_{max}=690$ nm); we interpret this finding as the first indication of partical formation of **7c**.

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Reversible Electrochemical Formation of Graphite Fluoride from Aqueous Hydrofluoric Acid**

By *Fritz Beck**, *Werner Kaiser*, and *Holger Krohn*

From the work of *Ruff* and *Rüdorff* it is known that graphite can form intercalation compounds of composition $(CF)_x$, $(C_4F)_x$, and $(C_n^+HF_2^-\cdot 2H_2F_2)_x$ with fluorine, where $n\geq 24$[1a,4]. They contain weakly bound fluorine and their high electrical conductivity changes little with the composition, up to saturation. The components are cheap and readily available. Compounds of this type are therefore interesting as positive active substances in galvanic cells. In terms of practical applications, graphite fluoride has been held to be sensitive to hydrolysis.

We have found that reversible electrochemical formation of graphite-fluorine intercalation compounds of the "salt type" $(C_n^+HF_2^-\cdot 2H_2F_2)_x$ from aqueous hydrofluoric acid over the concentration range 5—50 mol/L (10—100% wt) is possible. To date, it appears that this graphite salt can only be prepared in the absence of water[4].

In the overall equation (1), C and D signify "charge" and "discharge" (relative to the potential application as positive electrodes in accumulators):

$$(C_n)_x + 3x\,H_2F_2 \underset{D}{\overset{C}{\rightleftharpoons}} (C_n^+HF_2^-\cdot 2H_2F_2)_x + x\,H^+ + x\,e^- \qquad (1)$$

We have performed slow cyclovoltammetric measurements (voltage scan 1 mV/s) using CPP electrodes composed of 80% natural graphite flakes (94% "Kropfmühl Normalflocke") and 20% polypropylene. Measurements in 10 M and 25 M HF yielded the following:

Sharp increase in current after reaching a critical anode potential ("intercalation potential" E_I) whereby anodic intercalation occurs.

Limitation of the current density to *ca.* 5 mA/cm² arising from transport limitation in the CPP.

No overpotential in cathodic deintercalation in those cases where anodic intercalation occurs below 200 mV.

Reversible cyclizability at charge densities of 0.03—0.3 Ah/dm² at a 3 mm thick CPP electrode, whereby a formation effect is observed in the first cycle.

Ah yields of 90—100%.

We have already observed similar behavior with aqueous solutions of the acids H_2SO_4, $HClO_4$, and HBF_4[6]. Novel in the HF system is that the intercalation potential *linearly* decreases to a lesser extent than with other acids. Particularly positive intercalation potentials are therefore obtained with HF; with $c=10$ mol/L, E_I is 1.82 V (*vs.* SHE), whereas with the other acids the potential has fallen off to 1.24—1.43 V at the same concentration. Furthermore, in 70—90% HF, even at high overpotentials, reversible processes, which are absent in the other acids, were surprisingly found. This could signify a loading beyond $C_{24}F$.

Our results have considerable practical implications for the development of novel secondary cells with HF electrolytes. The battery metals M = Cu, Pb, Cd, Zn, and Mn in these electrolytes act as negative electrodes of the second kind. The overall reaction in the cycle is thus.

$$0.5x\,MF_2 + x\,H^+ + x\,e^- \underset{D}{\overset{C}{\rightleftharpoons}} 0.5x\,M + 0.5x\,H_2F_2 \qquad (2)$$

The sum of equations **1** and **2** indicates that on charging the cell 2.5 mol of H_2F_2 (as solvate acid) are consumed per Faraday. Because of the reversible behavior of the electrodes over a wide concentration range, this consumption is, however, not a limiting factor. To date, cyclic investigations with battery cells (Cu, Pb) have yielded over 1000 cycles (1 h charging at 3 mA/cm²) at small to intermediate conversions[8]. Stationary discharge potentials of 2.2 V, without a passivation tendency were observed with zinc as the negative electrode.

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Increasing interest has recently been shown in intercalation compounds for battery electrodes *e.g.* Li_xTiS_2. Examples of intercalated anions are relatively rare[13]. The possibility of using aqueous electrolytes facilitates practical applications.

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$[(CH_3)_5C_5Sn(C_5H_5N)]^+$: Synthesis, Structure and Bonding**

By *Peter Jutzi**, *Franz Kohl*, *Carl Krüger*, *Gotthelf Wolmershäuser*, *Peter Hofmann*, and *Peter Stauffert*

We recently reported on the synthesis, structure, and bonding of the *nido*-cluster $(CH_3)_5C_5Sn^+$[1,2]. The observed tendency of $(CH_3)_5C_5Sn^+CF_3SO_3^-$ to undergo covalent cation-anion interactions, and the existence of the covalent species $(CH_3)_5C_5Sn$—X (X = CF_3CO_2, CCl_3CO_2)[3] indicate the electrophilic character of the tin atom in the cluster cation. We have now succeeded in synthesizing an adduct of this species containing a nucleophilic neutral ligand.

On reaction of pentamethylcyclopentadienyltin trifluoromethanesulfonate **1**[3] with pyridine, the 1:1-adduct **2** is obtained as large, colorless crystals.

$$(CH_3)_5C_5Sn^+CF_3SO_3^- \xrightarrow[CH_2Cl_2]{C_5H_5N} [(CH_3)_5C_5Sn \leftarrow NC_5H_5]^+CF_3SO_3^-$$

1 → **2**

In the ^{1}H-NMR spectrum of **2** (in CH_2Cl_2, ext. TMS) the signals of the pyridine protons in the 2- and 4-positions are shifted downfield (relative to free pyridine); the singlet of the $(CH_3)_5C_5$-group of **2** ($\delta = 2.03$) appears at higher field than that of **1** ($\delta = 2.13$). Cryoscopic molecular weight determinations indicate the ionogenic character of **1** and **2** in solution (nitrobenzene). An X-ray structure analysis has been carried out on **2**[4] (Fig. 1).

The additional pyridine coordination compared to that in the free cluster cation[1,2] leads to a distortion towards a dihapto-structure within the $(CH_3)_5C_5Sn$ moiety. The Sn—C_{ring} bond lengths for C1 and C5 (adjacent to the pyridine) are shortest; as in η^5-$(CH_3)_5C_5Sn^+$, the methyl groups are tilted away from the ring plane of the central atom[1,2], the degree of tilting being greater, the shorter the length of the respective SnC bond. According to model calculations the observed weak coordination of the Sn-atom to one O-atom from each of the two anions (indicated by X in Fig. 1) is necessary in order to stabilize unsymmetric coordination of the five-membered ring and to prevent base-promoted loss of the pentamethylcyclopentadienyl ligand.

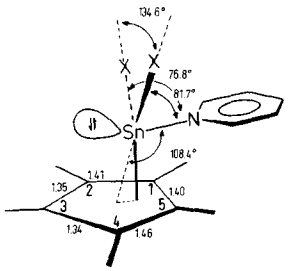

Fig. 1. Structure of **2** in the crystal (X = $CF_3SO_3^-$). The following SnC bond lengths were determined: Sn—C1 = 2.426 Å, Sn—C2 = 2.545 Å, Sn—C3 = 2.651 Å, Sn—C4 = 2.578 Å, Sn—C5 = 2.447 Å.

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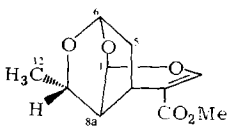
[3] F. Kohl, P. Jutzi, *Chem. Ber. 114* (1981) 488.
[4] Crystallographic data: Space group: monoclinic $P2_1/c$, $a = 8.627(1)$ Å, $b = 19.170(2)$ Å, $c = 12.024(1)$ Å, $\beta = 93.90(1)°$; solution: heavy atom method; total number of reflections: 6491, unobserved 2975 (20); $R = 0.047$, $R_w = 0.050$; residual density: 0.85 e/Å^3; anomalous dispersion for Sn and S was taken into consideration, H atoms found on the pyridine ring, on the CH_3-groups at calculated positions.

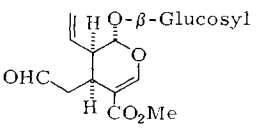
Stereocontrolled Synthesis of (+)-Sarracenin *via* Photochemical Cycloaddition**

By *Lutz-F. Tietze**, *Karl-Heinz Glüsenkamp*, *Masami Nakane*, and *C. Richard Hutchinson*

Sarracenin **1a** is a tricyclic monoterpene which has been isolated from the roots and leaves of the insectivorous plant *Sarracenia flava*[1]. **1a** is biologically closely related



1a [(−)-enantiomer]



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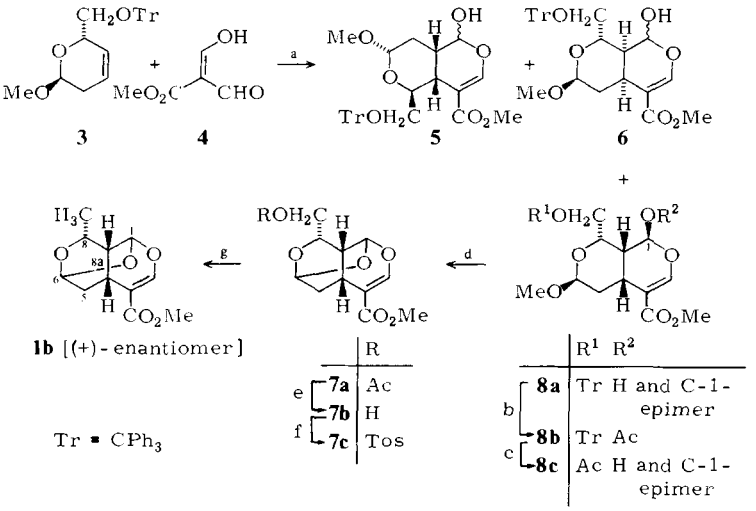
to the secoiridoid glycoside secologanin **2** and contains a dihydropyranyl ether group as characteristic structural element. We describe the synthesis of the enantiomerically pure (unnatural) (+)-sarracenin **1b**[4]. The key-step is the photochemical cycloaddition of the chiral olefin **3**[6], obtained in four steps from galactose in 31% yield, to methyl diformylacetate **4**[7].

Irradiation of **3** and **4** yielded the isomers **5** and **8a** as main products, together with **6**. Presumably $[_\pi 2 + _\pi 2]$-cycloadducts, which open *via* a retroaldol cleavage step to give the 1,5-dialdehydes and finally recyclize to give **5** (25%), **6** (5%), and **8a** (32%)[9], are involved as intermediates.

Further steps in the synthesis of (+)-sarracenin **1b**[11] starting from **8a** are illustrated in Scheme 1.



Scheme 1. a: 500 Watt Hg high pressure lamp, pyrex, **3**:**4** = 20:1 in cyclohexane, 9 h, 20°C; SC (silica gel; diisopropyl ether/cyclohexane = 3:1); **8a**: $R_f = 0.21$ (32%), $[\alpha]_D^{20} = +42$ ($c = 1$ in MeOH); **6**: $R_f = 0.17$ (5%); **5**: $R_f = 0.15$ (25%), m.p. = 215°C.—b: AcCl/pyridine/toluene 5 h, 20°C, 86% **8b**, m.p. = 209°C.—c: IR 120 ($H^{\oplus}$)/CH_2Cl_2, 35 h, 20°C, 84% **8c**.—d: HOAc/$HClO_4$, 8 min, 50°C, 77% **7a**, m.p. = 89°C.—e: MeOH/NaOMe, 30 min, 20°C, 94% **7b**, m.p. = 98°C.—f: TosCl/pyridine, 1 h, 20°C, 80% **7c**, m.p. = 143°C.—g: $NaBH_4$/DMSO, 90 min, 90°C, 61% **1b**, m.p. = 125°C.

The reaction sequence described is also suitable for the synthesis of secoiridoids which are functionalized at C-12.

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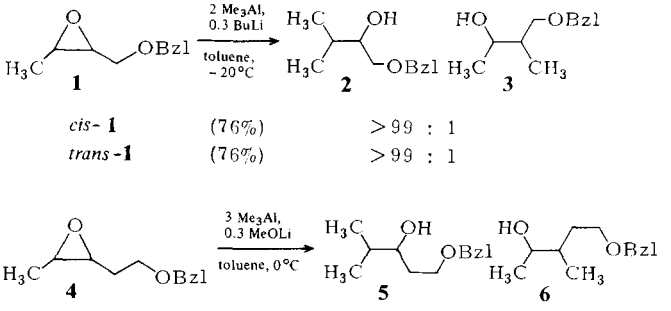
Angew. Chem. Suppl. 1982, 126

Regioselective Opening of α- and β-Alkoxyepoxides with Trimethylaluminum**

By *Andreas Pfaltz** and *Anton Mattenberger*

The development of efficient methods for the diastereo- and enantioselective epoxidation of allylic and homoallylic alcohols[1] has encouraged the use of α- and β-hydroxyepoxides as intermediates in the synthesis of acyclic systems[2]. Nucleophilic ring opening of these epoxides can lead to a wide variety of substituted alcohols. Such transformations are of particular interest when only one of the epoxide carbon atoms is attacked by the nucleophile[1d, 3].

We have investigated the reactions of various organometallic compounds with the α- and β-benzyloxyepoxides **1** and **4**. We have found that trimethylaluminum in the presence of catalytic amounts of butyllithium or lithium methoxide gives, respectively, the 1,2- and 1,3-dioxy compounds **2** and **5**. The regioisomeric alcohols **3** and **6** are only produced in trace amounts. Methylmagnesium bromide, methyllithium, lithium dimethylcuprate, or dimethylmagnesium react considerably less selectively. Pure trimethylaluminum reacts very slowly under the conditions given in Scheme 1[6]. Addition of catalytic amounts of butyllithium or lithium methoxide leads to a marked acceleration of the reaction. Hydrocarbons are particularly suitable solvents; ether or THF almost completely stop the reaction by forming complexes with the aluminum reagent.



Bzl = $CH_2C_6H_5$

Scheme 1.

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[6] C. R. Hutchinson, N. Nakane, unpublished results.

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[9] **8a**: ^{1}H-NMR ($CDCl_3$): $\delta = 1.15$–2.20 (m; 3 H, CH_2, 8a-H), 3.15 (mc; 1 H, 4a-H), 3.40 (s; 3H, OCH_3), 3.45 (mc; 2 H, CH_2), 3.65 (m; 0.3 H, α-OH), 3.72 (s; 3 H, OCH_3), 4.10 (d, $J = 8$ Hz; 0.7 H, β-OH), 4.25 (mc; 1 H, 8-H), 4.74 (d, $J = 3.6$ Hz; 0.7 H, 6-H), 4.82 (d, $J = 3.6$ Hz; 0.3 H, 6-H), 5.48 (t, $J = 8$ Hz; 0.7 H, 1-H); after H/D-exchange: 5.48 (d, $J = 8$ Hz; 0.7 H, 1α-H), 5.45 (m; 0.3 H, 1 β-H), 7.35 (mc; 16 H, 15 arom. H, 3-H).

[11] The assignment of five ^{1}H-NMR signals of **1a** in [1] must be altered in view of the double resonance experiments: 1-H: $\delta = 5.81$ (t, $J = 2$ Hz; 1 H); 6-H: $\delta = 5.02$ (d, $J = 3$ Hz; 1 H); 5-H_γ: $\delta = 2.36$ (br. dd, $J = 14$, 11 Hz; 1 H); 5-H_α and 8a-H: $\delta = 1.71$ (m; 2 H).

[1] a) P. A. Bartlett, *Tetrahedron 36* (1980) 3; b) M. R. Johnson, T. Nakata, Y. Kishi, *Tetrahedron Lett. 1979*, 4343, 4347; c) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc. 102* (1980) 5974; d) E. Hungerbühler, D. Seebach, D. Wasmuth, *Angew. Chem. 91* (1979) 1025; *Angew. Chem. Int. Ed. Engl. 18* (1979) 958.

[2] Cf. *e.g.* H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M. R. Johnson, Y. Kishi, *J. Am. Chem. Soc. 102* (1980) 7962; B. E. Rossiter, T. Katsuki, K. B. Sharpless, *ibid. 103* (1981) 464, as well as [1a, b].

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[**] Part of the Diplomarbeit from *A. M.* This work was begun during a period at Columbia University, New York. *A. P.* thanks Prof. *G. Stork* for encouragement and the Schweizerischer Nationalfonds for a fellowship.

[3] J. G. Buchanan, H. Z. Sable in B. S. Thyagarajan: Selective Organic Transformations, Vol. 2, Wiley-Interscience, New York 1972, p. 1; J. Fried, J. C. Sih, *Tetrahedron Lett. 1973*, 3899; S. Danishefsky, M. Y. Tsai, T. Kitahara, *J. Org. Chem. 42* (1977) 394.

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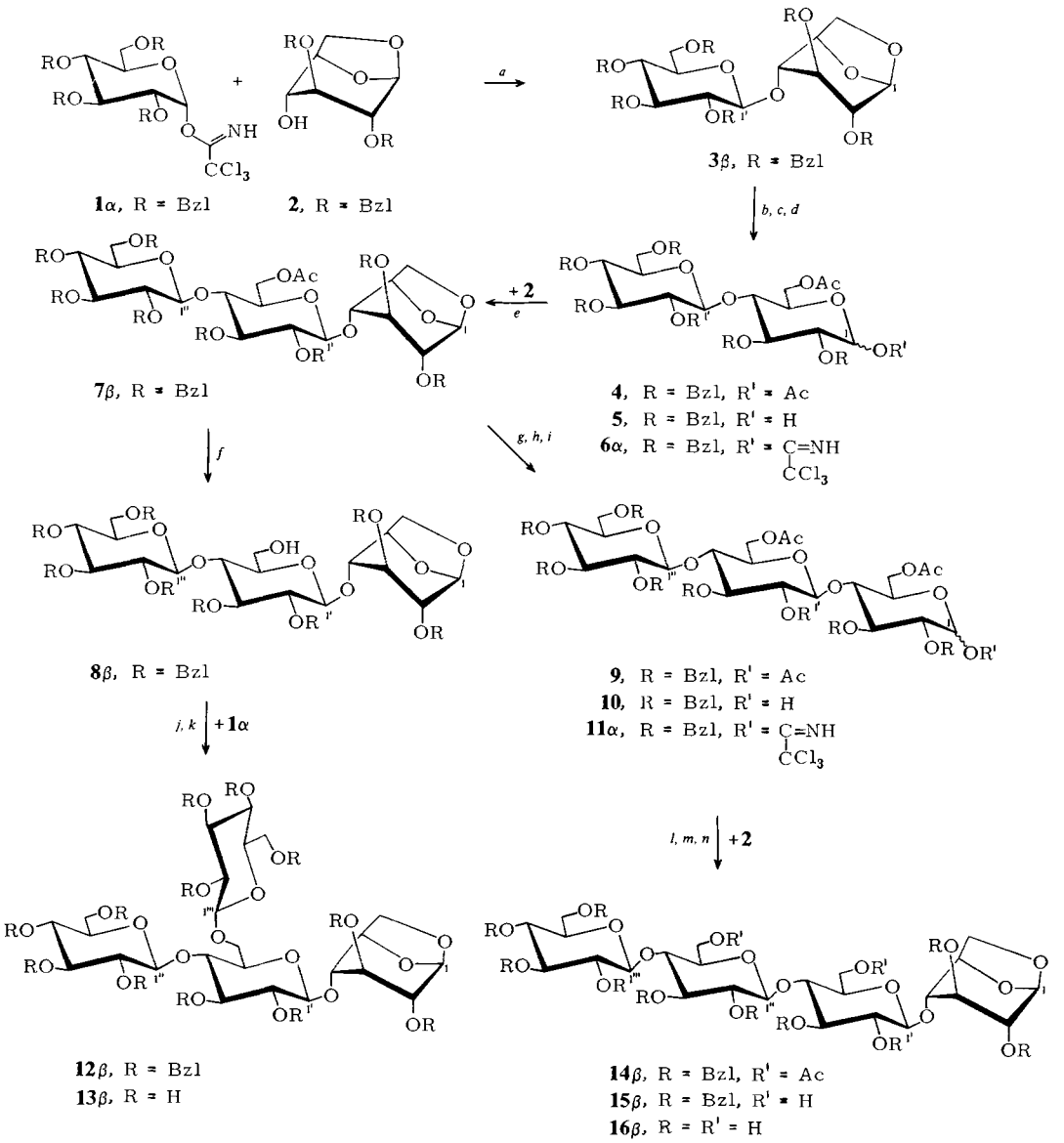
Synthesis of Linear and Branched Cellotetraoses**

By *Richard R. Schmidt** and *Josef Michel*

Versatile and efficient syntheses of 1,2-*trans*-β-glycopyranosides are a prerequisite for the synthesis of oligosaccharides[1]. Exclusively β-D-glucopyranosides are obtained when the α-trichloroacetimidate of 2,3,4,6-tetra-*O*-acetylglucopyranose is used as starting material[2]. We have now found that the conveniently accessible and isolable, but very reactive α-trichloroacetimidates **1α, 6α,** and **11α,** with benzyl protecting groups not capable of neighboring group participation, likewise react with high β-selectivity[3]. The ease with which the individual reaction steps can be carried out on a preparative scale enables, *e.g.*, the stepwise synthesis of the branched and linear cellotetraose derivatives **12β** and **13β,** and **14β, 15β** and **16β,** respectively (Scheme 1)[4]. The intermediates thus formed are extremely useful synthons for block syntheses[5].



Scheme 1. *a:* 0.05 equiv. $BF_3 \cdot OEt_2$ in CH_2Cl_2, −38 °C, 2.0 h; yield 90% **3β** : **3α** ≈ 10 : 1.—*b:* CF_3COOH in HOAc/Ac_2O, RT, 2.5 h; yield 84% **4** (α,β-mixture).—*c:* $C_6H_5CH_2NH_2$ in Et_2O, RT, 1.5 h; yield 90% **5**.—*d:* Cl_3CCN/NaH in CH_2Cl_2, RT, 3 h; yield 93% **6α** : **6β** ≈ 11 : 1.—*e:* 0.1 equiv. $BF_3 \cdot OEt_2$ in CH_2Cl_2, −40 °C, 2 h; yield 57% **7β**.—*f:* NaOMe in MeOH/Et_2O, RT, 5 h; yield 96% **8β**.—*g:* CF_3COOH in HOAc/Ac_2O, RT, 2.5 h; yield 76% **9** (α,β-mixture).—*h:* $C_6H_5CH_2NH_2$, RT, 2.5 h; yield 80% **10**.—*i:* Cl_3CCN/NaH in CH_2Cl_2, RT, 5 h; yield 96% **11α** : **11β** ≈ 5 : 1.—*j:* 0.1 equiv. $BF_3 \cdot OEt_2$ in CH_2Cl_2, −35 °C, 2.5 h; yield 70% **12β** : **12α** ≈ 6 : 1.—*k:* Pd-black/H_2 in MeOH/CH_3COOEt/HOAc; yield 96% **13β**.—*l:* 0.5 equiv. $BF_3 \cdot OEt_2$ in CH_2Cl_2, −35 °C, 5 h; yield 40% **14β**.—*m:* NaOMe in MeOH/Et_2O, RT, 4 h; yield 95% **15β**.—*n:* Pd-black/H_2 in MeOH/CH_3COOEt/HOAc; yield 92% **16β**.—Bzl = Benzyl.

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Angew. Chem. Suppl. 1982, 78

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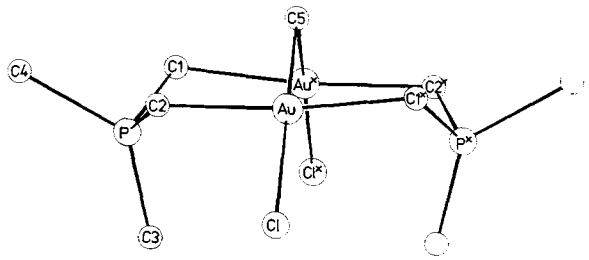


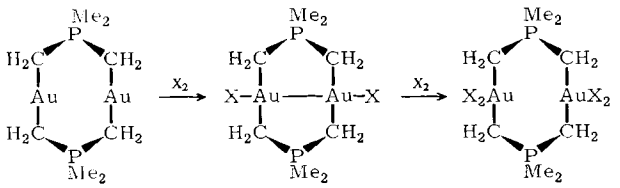
Fig. 1. Structure of μ-methylenebis[μ-dimethylphosphoniodimethanido]-dichlorodigold(III) **4a** (structure of "A frame type" [5]).

Methylene Bridging of two Gold Atoms through Double Oxidative Addition of Methylene Dihalides to a Cyclic Ylide Complex**

By *Petr Jandik, Ulrich Schubert,* and *Hubert Schmidbaur**

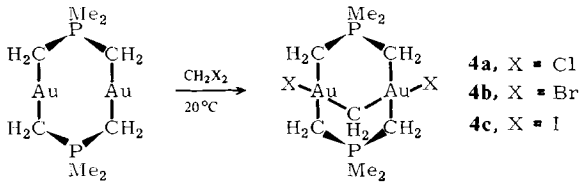
Gold(I) compounds easily undergo oxidative addition.

In the first step of the addition of halogen to binuclear cyclic ylide complexes[2,3] **1**, a transannular gold(II)—gold(II) bond, which subsequently may be cleaved again by excess halogen to give classical gold(III) compounds[2-4] **3**, is observed in the intermediate **2** (Me = methyl).



1 **2** **3**

We now report on the addition of methylene dihalides to the heterocycle **1**, leading to formation of bridged bicyclic compounds.



4a, X = Cl
4b, X = Br
4c, X = I

1

The reaction proceeds even at room temperature in 60—65% yield, and the resulting crystalline, air-stable compounds **4** are virtually free of by-products.

The structures of the new compounds **4a—c** have been confirmed by an X-ray diffraction analysis of **4a** (Fig. 1), as well as by elemental analyses, mass spectra, ^{1}H-, ^{13}C-, and ^{31}P-NMR spectra. The non-equivalence of the methyl groups at each phosphorus atom and of the hydrogen atoms in each PCH_2Au bridge is diagnostic, as is the magnetic equivalence of the P atoms and of the two H atoms of the $AuCH_2Au$ bridge (C_{2v} symmetry).

Molecular ions appear in the EI mass spectra, along with fragments stemming from loss of halogen, and the heterocycle **1**. In the IR spectrum of **4a**, ν(AuCl) is located at 262 cm^{-1}. A band at 360 cm^{-1} is characteristic of the $AuCH_2Au$ bridge in all three homologues.

The thermal stability of the compounds **4a—c** is surprisingly high (decomp. at *ca.* 200 °C). They are also chemically relatively recalcitrant, and complex **4a**, which is insoluble in most other solvents, is soluble in trifluoroacetic acid and can be stored in this solution at room temperature for several days without decomposition (NMR solvent).

The oxidative addition of CH_2X_2 to binuclear complexes described here (cf. Supplement) is of particular interest, since to the best of our knowledge it is the first reported example in which *both* C—X bonds are involved; previously only the formation of halomethyl derivatives could be achieved[7].

$$M + CH_2X_2 \rightarrow X—M—CH_2X$$

This type of reaction is currently of great interest[8].

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[**] This work was supported by the Deutsche Forschungsgemeinschaft, Hoechst AG, Degussa AG, and the Verband der Chemischen Industrie.

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Activation of Silanes on a Ruthenium Cluster: Synthesis, Characterization, and Catalytic Action of the Cluster Anion $[HRu_3(CO)_{10}(SiEt_3)_2]^-$

By *Georg Süss-Fink**

In the course of the rapid development in homogeneous catalysis, considerable interest has been focused on syntheses involving silanes[1]. In order to understand the basic catalytic processes of these reactions, the activation of the

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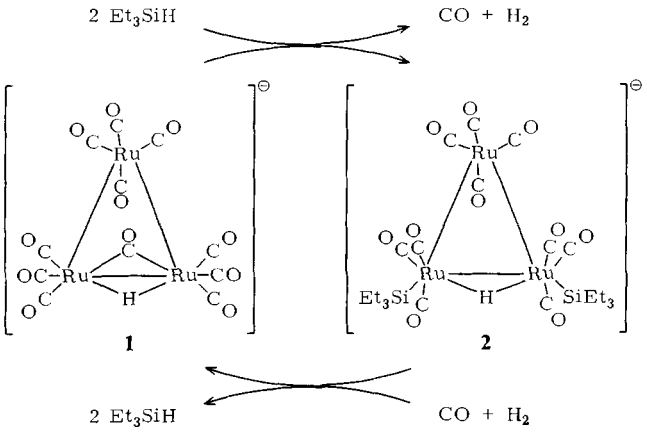
silane molecule on transition metal complexes is of significance.

The novel cluster anion **2** is formed by reacting the cluster anion **1** with triethylsilane in tetrahydrofuran (THF) solution; gas chromatographic analysis of the reaction gas shows that CO and H_2 are liberated.

$$\underset{\mathbf{1}}{[HRu_3(CO)_{11}]^-} + 2\,Et_3SiH \xrightarrow{THF} \underset{\mathbf{2}}{[HRu_3(CO)_{10}(SiEt_3)_2]^-} + CO + H_2$$

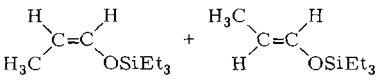
The reaction proceeds almost quantitatively at room temperature. The anion **2** can be isolated as the bis(triphenylphosphoranediyl) ammonium salt $[N(PPh_3)_2][HRu_3(CO)_{10}(SiEt_3)_2]$ (slightly air-sensitive red crystals). This formula is consistent with the results of elemental analysis, molecular weight determination, and conductivity measurements. IR- and NMR-data [$^1H(CD_3COCD_3$, $-75\,^\circ C$): $\delta = 7.64$ (m, 30H), 0.98 (m, 30H), -18.46 (s, 1H); ^{13}C, ^{29}Si] suggest that **2** consists of an isosceles Ru_3-triangle with a hydride bridge and a silyl group at each bridgehead atom.

In the presence of CO and H_2 under pressure, **2** is converted back into **1**, which upon reduction of pressure reacts again with the liberated Et_3SiH to give **2**.



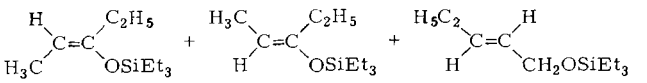
This equilibrium apparently is decisive for the catalytic action of **1** and **2**: In THF under mild conditions **1** or **2** catalyzes the reaction of ethylene, CO, and triethylsilane to the unsaturated silyl ethers **3**—**7**.

$$H_2C{=}CH_2 + CO + Et_3SiH \longrightarrow$$



3, 29% **4**, 21%

$$2\,H_2C{=}CH_2 + CO + Et_3SiH \longrightarrow$$



5, 7% **6**, 6% **7**, 12%

After reaction, the solution contains—irrespective of whether **1** or **2** were employed—a mixture of **1** and **2**, which remains catalytically active in subsequent reactions.

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Angew. Chem. Suppl. (1982) 71

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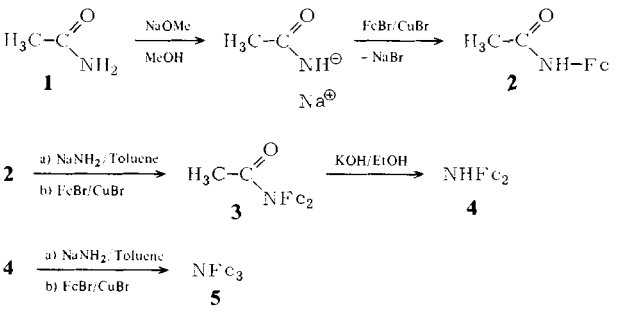
Triferrocenylamine, NFc_3

By *Max Herberhold**, *Max Ellinger*, *Ulf Thewalt*, and *Friederike Stollmaier*

We report here on the preparation, characterization, and X-ray structural analysis of the tertiary amine triferrocenylamine, NFc_3 **5** (Fc = ferrocenyl = $-C_5H_4FeC_5H_5$).

Using acetamide **1** as starting material, three ferrocenyl substituents were stepwise attached to the nitrogen atom as shown below.



The intermediates **3** and **4** were first obtained by *Nesmeyanov et al.*[2]. Further ferrocenylation of **4** with ferrocenyl bromide/copper(I) bromide gave **5** in the form of reddish brown, air-stable crystals. **5** was identified on the basis of elemental analysis and its ^1H-NMR, ^{13}C-NMR, and mass spectra.

According to an X-ray structural analysis the arrangement around the central N-atom in **5** is almost planar; the N-atom is only about 6 pm out of the plane of the directly bonded C-atoms (C1, C11, and C21) (Fig. 1). The three ferrocenyl groups are oriented differently with respect to this plane—but not in a propeller-like fashion. The amine **5** no longer reacts basically.

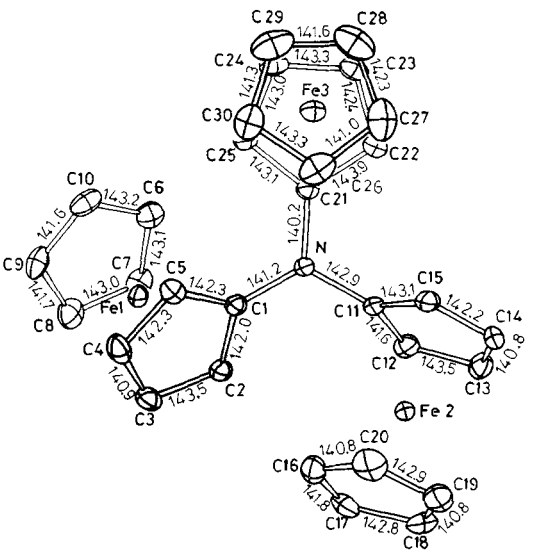


Fig. 1. Molecular structure of NFc_3 **5** in the crystal, projected on the C1, C11, C21 plane. The errors in the distances amount to 0.6 pm.

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Table 1 presents characteristic structural data of ammonia and some tertiary amines. Corresponding to the type of substituents on the N-atom, the NC_3-pyramid becomes increasingly planar along the series $N(CH_3)_3$-$N(C_6H_5)_3$-NFe_3 **5**.

Table 1. Structural data of ammonia and some tertiary amines: *h* is the distance of the N-atom from the plane of the three directly bonded neighboring atoms.

	NH_3	$N(CH_3)_3$ [8a]	$N(C_6H_5)_3$ [9]	NFe_3 **5**
d(N—H) [pm]	101.5			
d(N—C) [pm]		145.1(3)	142(4)	141.4
∢ NHN [°]	106.6			
∢ CNC [°]		110.9(6)	116(2)	119.8
h [pm]	38	45	23	6

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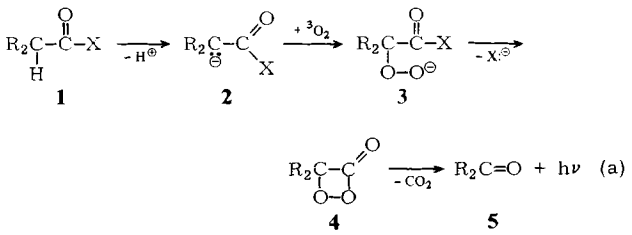
Formation of $^1O_2$ in the Reversible Autoxidation of Enolates Derived from Carboxylic Acids**

By *Waldemar Adam**, *Omar Cueto*, and *Hector Rebollo*

Oxidative decarboxylation of carboxylic acids is one of the important metabolic processes that leads to the next lower homolog[1]. The general mechanism is given in [eq. (a)][2]. Previously we have been concerned with the mechanistic details of step **4**→**5**, and through model studies we showed that α-peroxylactones **4** are the "high energy"



intermediates responsible for light emission[3]. Presently we have turned our attention to step **2**→**3**, in the hope of elucidating its mechanism. Our model experiments on diphenylacetic acid **1a** (R = C_6H_5, X = OH) and isobutyric acid **1b** (R = CH_3, X = OH) show that

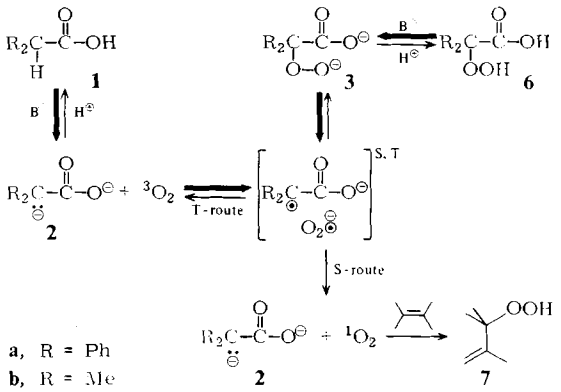
1) the oxygenation of the carboxylate dianion **2** (X = $O^\ominus$) is reversible and
2) $^1O_2$ is formed in the reverse process **3**→**2**.

Treatment of a 0.1 M solution of **1a** in tetrahydrofuran (THF) with 2 equivalents of *n*BuLi at −78 °C produced **2a** quantitatively (100% α-deuteration with D_2O). After oxygenation with $^3O_2$ and protonation with HCl at −78 °C, pure **6** was isolated in 80% yield[4]. Only *ca.* 5% of **1a** could be detected by ^{1}H-NMR. When a solution of **3a** in THF was warmed up over 2h to 25°, held there for 60 min and protonated with HCl, the yield of **1a** was *ca.* 12%, along with *ca.* 24% decomposition products of **3a** (benzophenone, benzilic acid).

Deprotonation of a 0.1 M solution of **6a** in THF with *n*BuLi or lithium diisopropylamide at −78 °C, followed by warming (see above), maintainance of this temperature for 60 min, and protonation with HCl gave *ca.* 13% **1a** along with *ca.* 30% benzophenone and benzilic acid. If a solution of 0.5 M tetramethylethylene (TME) in THF was added to the reaction mixtures from **1a** or **6a** before they were warmed up to 25 °C, after protonation with HCl, 6—8% **7** was obtained, and was identified by comparison with authentic material. Similarly under these conditions **6b** gave *ca.* 1.5% **1b** and 2.5% **7**.

7 is in fact a product of $^1O_2$ oxygenation since at 25 °C $^3O_2$, either alone or with *n*BuLi does not convert TME into **7**, but addition of **2a** to a solution of TME in THF at −60 °C through which $^3O_2$ was bubbled did. TME did not produce **7** on treatment with KO_2 at 25 °C.

Double deprotonation of **6b** under the above conditions produces 1.5% **1b** and 2.5% **7**. Since the direct reaction of **2** with $^3O_2$ to give the α-peroxy dianion **3** is spin forbidden, the oxygenation **2**→**3** must proceed stepwise *via* one-electron transfer to give the superoxide ion-enolate radical anion cage. Cage recombination and subsequent protonation lead to the α-hydroperoxy carboxylic acid **6** (Scheme 1). In competition with the formation of **3**, the radical cage can release $^3O_2$ (T route) or form $^1O_2$ (S route). Alternatively, the radical cage can be generated by double deprotonation of **6**.



Scheme 1.

In conclusion, the α-oxygenation of enolates provides a hitherto unprecedented potential source of $^1O_2$. In view of the serious pathological effects of $^1O_2$, it seems relevant to demonstrate its involvement in enzymatic autoxidations.

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How Similar are Tropoquinones and Benzoquinones?**

By *Rolf Gleiter**, *Walter Dobler*, and *Mirjana Eckert-Maksić*

4,6-Cycloheptadiene-1,2,3-trione **1**[1] and 3,6-cycloheptadiene-1,2,5-trione **2**[2] are structural isomers which have been designated *o*-tropoquinone and *p*-tropoquinone due to their analogy with *o*-benzoquinone **3** and *p*-benzoquinone **4**. In order to determine *de facto* how far the similarity applies, we recorded the He(I) photoelectron (PE) spectra of **1** and **2** and compared those with the PE spectra of **3**[3] and **4**[4] (cf. Fig. 1).

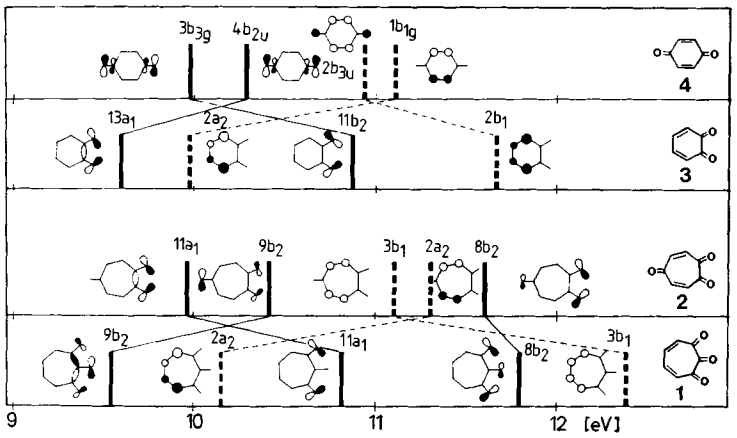

Fig. 1. Comparison of the first PE bands of **1**–**4**.

The PE spectra of the *p*-quinones **4** and **2** (cf. Fig. 1) contain closely spaced bands which correspond to ionizations from the n orbitals ($3b_{3g}$, $4b_{2u}$ for **4**, and $11a_1$, $9b_2$ for **2**) and the π orbitals ($2b_{3u}$, $1b_{1g}$ for **4**, and $3b_1$, $2a_2$ for **2**). In contrast, in the *o*-quinones **3** and **1** the bands corresponding to ionization from n orbitals ($13a_1$, $11b_2$ for **3**, and $9b_2$, $11a_1$ for **1**) and π orbitals ($2a_2$, $2b_1$ for **3** and $2a_2$, $3b_1$ for **1**) are widely separated from each other. The great similarity between benzoquinones and tropoquinones with respect to the position of the cationic states (Fig. 1) depends upon the fact that the relative energies and the wave functions of the n and π orbitals are comparable in both systems.

A similar conclusion can also be drawn from a comparison of the first excited states: a similar hypsochromic shift is observed between the 1st bands of the absorption spectra of **3** (16400 cm^{-1})[8] and **4** (21800 cm^{-1})[8] and the corresponding bands of **1** (17800 cm^{-1})[1] and **2** (22700 cm^{-1})[2].

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Oxanickelacyclopentene Derivatives from Nickel(0), Carbon Dioxide, and Alkynes

By *Georg Burkhart* and *Heinz Hoberg**

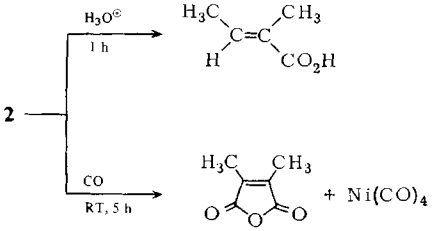
We have extended our investigations of the nickel(0) hetero-1,2-diene system[1–4] to carbon dioxide. We have found that nickel(0) in combination with the strongly basic chelating ligand *N,N,N',N'*-tetramethylethylenediamine (Me_4en) causes disproportion of CO_2 to $(Me_4en)Ni(CO_3)$ **1** and tetracarbonylnickel (cdt = 1,5,9-cyclododecatriene).

$$5\ (cdt)Ni + 8\ CO_2 \xrightarrow[RT,\ 72\ h]{+\ Me_4en} 4\ (Me_4en)Ni(CO_3) + Ni(CO)_4$$
1

In the presence of 2-butyne, disproportionation does not occur and the oxanickelacyclopentene derivative **2** is formed. [Yield 65%; m.p. = 170 °C (decomp.); IR(KBr): 1620 (νCO), 500 cm^{-1} (νNiO)].

$$(cdt)Ni + H_3CC{\equiv}CCH_3 + CO_2 \xrightarrow[RT,\ 48\ h]{+\ Me_4en} (Me_4en)Ni$$
2

Protonolysis of **2** led to 2-methylcrotonic acid, and reaction of **2** with carbon monoxide gave dimethylmaleic anhydride and tetracarbonylnickel.



Compounds of type **2** are potential intermediates in the nickel-catalyzed synthesis of 2-pyrone from alkynes and carbon dioxide[6].

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Angew. Chem. Suppl. 1982, 147

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A 1,2-Dithiolenenickel Complex with Different Substituents—a Novel Type of Mixed-Valence Compounds**

By *Arnd Vogler** and *Horst Kunkely*

Mixed-valence (intervalence (IT)) compounds[1] are distinguished, among other characteristics, by unusual bands in their absorption spectra. If the metal-metal interaction is weak, definite oxidation states can be assigned to the metals, and charge transfer (CT) electronic transitions from reduced to oxidized metal occur at relatively low energies. The associated IT absorption bands lie in the long wavelength spectral region, frequently in the near IR, and their position is solvent dependent.

Mononuclear metal complexes, in which a ligand occurs in different oxidation states ($L_{red}ML_{ox}$), can also be viewed as IT compounds. In this case too, CT electronic transitions from the reduced to the oxidized ligands should be possible. No IT absorption bands can be detected in complexes having catecholate and *o*-semiquinone as IT-ligands[2]. Mixed valence ligands are also present in the 1,2-dithiolene complexes of Ni^{II}, Pd^{II}, and Pt^{II}.

When R = R′ the ground state is described by the two resonance forms **A** and **B**[3]; both the highest occupied ($2b_{1u}$) and the lowest unoccupied ($3b_{2g}$) ligand orbitals—both are not degenerate—are delocalized over both ligands[3]. In consequence, the $3b_{2g} \leftarrow 2b_{1u}$ electronic transition has no CT contribution and the position of the associated absorption band is not dependent on the solvent. The complexes are not mixed-valence compounds.

The resonance form **B** (R = CN, R′ = C_6H_5) contributes strongly to the ground state of the complex

$[Ni\{S_2C_2(CN)_2\}\{S_2C_2(C_6H_5)_2\}]$ **1**

This assumption is consistent with the observation that homogeneous complexes with R = R′ = CN are considerably more difficult to oxidize than those with R = R′ = C_6H_5[4]. The donor orbital $2b_{1u}$ is more strongly localized on the ligand with R = CN, and the acceptor orbital $3b_{2g}$ more strongly localized on the ligand with R′ = C_6H_5. The electronic transition between both orbitals, therefore, possesses more CT character and the position of the associated absorption band should depend on the solvent.

1 is not stable, however, the anion $\mathbf{1}^{\ominus}$[4] is; in the latter compound the acceptor orbital $3b_{2g}$ is singly occupied, but the electronic transition $3b_{2g} \leftarrow 2b_{1u}$ is still possible. The typical, intense longwave absorption band (Fig. 1) is dependent upon the solvent. For the solvents chlorobenzene, chloroform, pyridine, dimethyl sulfoxide, and acetonitrile a linear plot of the wavenumber of the maximum *vs.* $1/n^2 - 1/D$[1] (n^2 and D are, respectively, the optical and static dielectric constants of the solvent) is obtained with a slope of 440 cm^{-1}. The solvent dependence is certainly much smaller than that of the "mixed" 1,2-dithiolatediimine complexes of Ni^{II}[5] and Pt^{II}[6], in whose ground state the resonance form with dithiolate and diimine as ligands almost exclusively occurs.

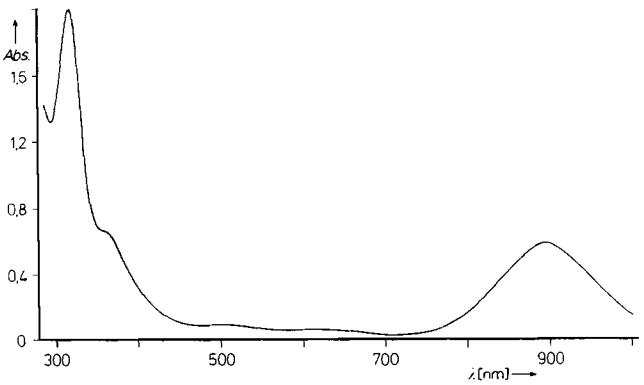

Fig. 1. Absorption spectrum of $\mathbf{1}^{\ominus}$ ($c = 6.75 \cdot 10^{-5}$ mol/L, CH_3CN, 1 cm cuvette).

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Intervalence Transfer between Hexaaminecobalt(III) and Hexacyanoruthenate(II)**

By *Arnd Vogler** and *Josef Kisslinger*

A distinction is made between outer-sphere and inner-sphere redox reactions in thermal electron transfer between transition-metal complexes[1]; optical charge-transfer transitions (CT) between a reducing and an oxidizing metal center can be observed (intervalence transfer, IT)[2], either if both metals are bonded *via* bridging ligands in a dinuclear complex (inner-sphere) or are in close contact in separated metal complexes (outer-sphere), *e.g.* as ion-pairs[3]. Until now, inner- *and* outer-sphere IT-transitions in *one* system have never been observed. We have previously investigated the dinuclear complex $[(NH_3)_5Co^{III}(\mu\text{-}NC)Ru^{II}(CN)_5]^-$ **1**[4] and now describe the ion-pair $[Co(NH_3)_6]^{3+}/[Ru(CN)_6]^{4-}$, the mononuclear components of **1**.

Earlier attempts to study $[Co(NH_3)_6]^{3+}/[Ru(CN)_6]^{4-}$ in solution were thwarted by the fact that $[Co(NH_3)_6]_4[Ru(CN)_6]_3$, which is insoluble in all the usual solvents, immediately precipitates out. We have now found that supersaturated solutions, from which the difficultly soluble precipitate is first formed after several hours, are formed from mixtures of not too concentrated solutions ($c < 5 \times 10^{-3}$ mol/L) of $[N(C_2H_5)_4]_4[Ru(CN)_6]$ and $[Co(NH_3)_6]^{3+}(CH_3CO_2^-)_3$ in dimethyl sulfoxide (DMSO).

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Whereas the absorption spectra of both separated mononuclear complexes only contain both the ligand-field bands of $[Co(NH_3)_6]^{3+}$ above 300 nm ($[Ru(CN)_6]^{4-}$ first absorbs below 300 nm), the supersaturated solution of the ion-pair $[Co(NH_3)_6]^{3+}/[Ru(CN)_6]^{4-}$ in DMSO exhibits, apart from the ligand field band, (shoulder at 475 nm), a novel band with $\lambda_{max} = 360$ nm, which we assign to the IT transition from reducing Ru^{II} to oxidizing Co^{III} (Fig. 1). Since at concentrations between 5×10^{-3} and 1×10^{-3}

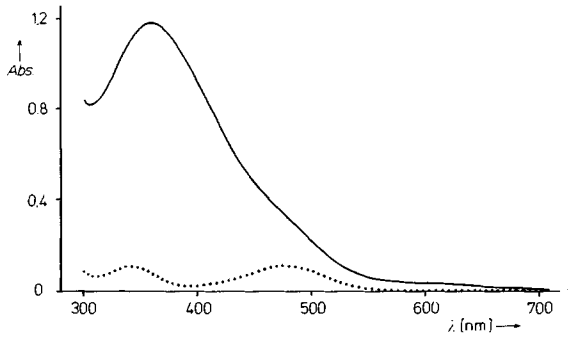

Fig. 1. Absorption spectrum of $[Co(NH_3)_6](CH_3CO_2^-)_3$ ($c = 2 \times 10^{-3}$ mol/L) alone (.....) and together with $[N(C_2H_5)_4]_4[Ru(CN)_6]$ (2×10^{-3} mol/L) (——) in DMSO.

mol/L the Beer/Lambert law applies, we presume that complete ion-pairing occurs; the maximum of the IT absorption has an extinction coefficient $\varepsilon = 580$. The width at half-height $\Delta\tilde{\nu}_{1/2} = 10870$ cm^{-1} is approximately a factor of 1.5 larger than the theoretical value calculated according to *Hush*[2]:

$$\Delta\tilde{\nu}_{1/2}(\text{theor.}) = (2310\,\tilde{\nu}_{max} - \Delta E)^{1/2} = 7085 \text{ cm}^{-1}$$

Thereby, $\tilde{\nu}_{max}$ is the wavenumber of the IT band at the maximum, and ΔE the energy difference of the system in thermal equilibrium, before and after the electronic transition:

$$[Co(NH_3)_6]^{3+}/[Ru(CN)_6]^{4-} \xrightarrow{\Delta E} [Co(NH_3)_6]^{2+}/[Ru(CN)_6]^{3-}$$

ΔE was calculated from the standard potentials of $[Co(NH_3)_6]^{3+/2+}$ ($E_0 = +0.11$ V)[5] and $[Ru(CN)_6]^{3-/4-}$ ($E_0 = +0.86$ V)[5]. A similar difference between theoretical and experimental widths at half-height has been observed for the IT bands of other systems[2].

It is astonishing that the absorption spectrum of the ion-pair is very similar to that of the dinuclear complex **1** (IT band: $\lambda_{max} = 375$ nm, $\varepsilon = 690$, $\Delta\tilde{\nu}_{1/2} = 7980$ cm^{-1})[4]. It therefore follows that the inner-sphere- and outer-sphere-IT interactions are of similar magnitude. The small long-wavelength shift of the IT band in **1** may be traced back to the short distance between both metal ions[2]. In the ion-pair, Co^{III} and Ru^{II} are separated by a cyanide and an ammonia ligand, and in **1** only by a cyanide ligand.

Irradiation ($\lambda = 366$ nm) of the ion-pair results, as with the bridged complex, in a photoredox reaction (quantum yield: $\phi = 0.034$):

$$[Co(NH_3)_6]^{3+} + [Ru(CN)_6]^{4-} \rightarrow Co^{2+} + 6\,NH_3 + [Ru(CN)_6]^{3-}$$

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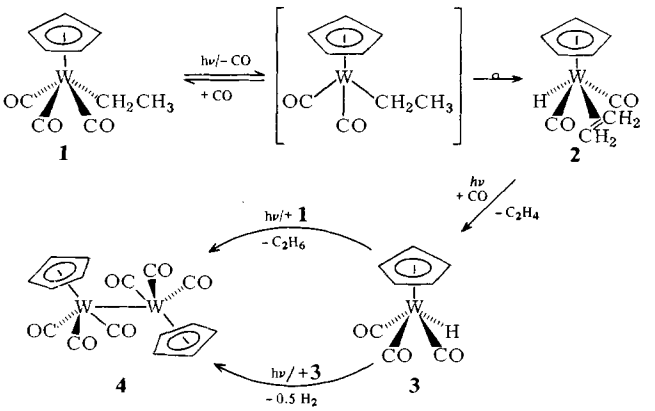
Preparation of an Ethylene(hydrido)tungsten Complex by Photo-Induced β-Elimination**

By *Helmut Guido Alt** and *Manfred Erwin Eichner*

The β-elimination reaction is considered to be a typical "decomposition" pathway for alkyl transition-metal complexes having alkyl ligands with more than one C atom. In many instances, dealkylations of this type are plausible thermal decompositions[1] and are presumed to occur in some photo-induced reactions[2]. Reversible dealkylation of some transition-metal complexes is involved in many important industrial processes with olefins, *e.g.* homogeneously catalyzed hydroformylation, hydrogenation, or isomerization. We have now succeeded in isolating the intermediates **2** and **3**, which are characteristic of β-elimination, by photolyzing the thermally stable ethyl complex **1** in solution.



The rate determining step is the reversible CO cleavage from **1**. In the presence of CO, a drastic retardation of the photolysis is observed; phosphanes and phosphites (L) form the substitution products $C_5H_5W(CO)_2(L)Et$[3]. Continuous removal of the cleaved CO by gaseous means (Ar, N_2, H_2) increases the fraction of **2**; the highest yield (6%) was obtained by passing ethylene through the solution. The ethylene(hydrido) complex **2** (decomp. 70 °C) was characterized spectroscopically [IR (pentane): ν(CO) = 1978 s, 1903 vs cm^{-1}; ^{1}H-NMR ([D$_6$] acetone, room temperature): $\delta = 5.43$ (C_5H_5, s, 5), 2.00 (C_2H_4, s, br, 4), −5.71 (*H*, s, br, 1); ^{13}C-NMR ([D$_6$]acetone): $\delta = 90.6$ (C_5H_5), 218.8 (*C*O), 21.1 (C_2H_4); MS: *m/z* 334 (M^+) relative to ^{184}W. The ethylene ligand—similar to that in $C_5H_5W(CO)_2(C_2H_4)CH_3$ and its indenyl analog[4]—exhibits intramolecular motion.

Proof that exclusive H_β migration is responsible for the reaction of **1**→**2** is provided by the photolysis of

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$C_5H_5W(CO)_3CD_2CH_3$. The work-up of this reaction gives only **3** and no $C_5H_5W(CO)_3D$. The formation of ethane is interpreted by the photo-induced reaction of **3** with **1**. The molybdenum analogue of **2** was observed by IR spectroscopy [ν(CO) = 1985 s, 1901 vs] in the photolytic degradation of $C_5H_5Mo(CO)_3Et$ in solution; however, no olefin(hydrido) complex could be isolated.

Procedure

2 (All operations were performed under Ar using anhydrous solvents): A solution of **1** (1300 mg, 3.6 mmol) in 250 mL of pentane was irradiated with an Hg high-pressure lamp (Hanovia L 450 W) for 10 min at −20 °C while ethylene was passed in. The filtrate of the suspension was placed on a frit covered with a 5 cm thick layer of silica gel. **1** and **2** were eluted at −10 °C using pentane. Fractional crystallization at −78 °C yielded **2** as brown crystals (75 mg ≙ 6%).

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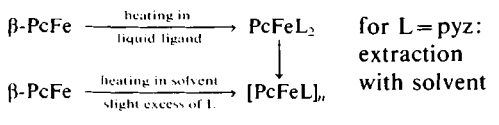
A Novel Type of Organic Conductor: One-Dimensionally Polymerized Phthalocyaninatoiron(II)**

By *Otto Schneider* and *Michael Hanack**

Phthalocyaninato(μ-pyrazine)iron(II), $[PcFe(pyz)]_n$, **1a**, the first phthalocyaninatoiron(II) polymerized *via* a bidentate bridging ligand, has an electric conductivity of up to 10^7 times higher than that of the monomer $PcFe(pyz)_2$[2]. Consistent with our new concept[3], increases in conductivity should also be achieved with other linear, π electron-rich bridging-ligands L by polymerization.

We obtained the polymers **1a-c** and the monomers $PcFe(bpy)_2$ **2** and bis(benzylisocyanide)phthalocyaninatoiron(II), $PcFe(bzNC)_2$, as follows:

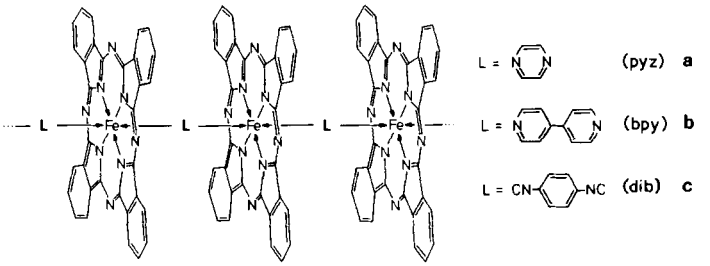


The products were characterized by thermogravimetry (TG)/differential thermal analysis (DTA) and by IR/FIR and UV/VIS/NIR measurements.

$$PcFeL_x \xrightarrow{\Delta} PcFe + xL \qquad (x = 1, 2)$$

According to TG/DTA measurements the thermal stability of these compounds increases along the series:

$PcFe(pyz)_2$ < $PcFe(bzNC)_2$ < $PcFe(bpy)_2$ **2** ≈ $[PcFe(bpy)]_n$ **1b** < $[PcFe(dib)]_n$ **1c** ≈ $[PcFe(pyz)]_n$ **1a**
(bz = $C_6H_5CH_2$)



1a-1c

The effect of the increase in conductivity is achieved without additional doping[19] and, in these new compounds, does not appear to be dependent, or if so only slightly, on the length of the linear, bidentate bridging ligands (Table 1).

Table 1. (Selected data). Electrical direct current dark conductivities measured on compressed pellets by the 2-probe technique (2 kbar) or (**1a** and **1c**) by the 4-probe technique (1 kbar).

	σ_{RT} [$\Omega^{-1}\cdot cm^{-1}$]		σ_{RT} [$\Omega^{-1}\cdot cm^{-1}$]
β-PcFe	$4\cdot10^{-11}$	**2** $PcFe(bpy)_2$	$5\cdot10^{-13}$
$PcFe(pyz)_2$	$2\cdot10^{-12}$	**1b** $[PcFe(bpy)]_n$	$2\cdot10^{-8}$
1a $[PcFe(pyz)]_n$	$2\cdot10^{-5}$	$PcFe(bzNC)_2$	$2\cdot10^{-12}$
$PcFe(bpy)_2\cdot1bpy$	$3\cdot10^{-12}$	**1c** $[PcFe(dib)]_n$	$2\cdot10^{-5}$

Doping **1a** with iodine leads to $[PcFe(pyz)I_2]_n$, whose conductivity is $1\times10^{-2}\ \Omega^{-1}\ cm^{-1}$.

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α,β-Unsaturated Ketones by Cathodic Addition of Benzotrichloride to Ketones**

By *Michael Steiniger* and *Hans J. Schäfer**

Organic halides can be reductively added to activated double bonds to give cyclopropanes[1] or to carbonyl compounds to give alcohols[2] or olefins[3]. We have now found that α,β-unsaturated phenylketones (eq. 1) can be prepared in good yields in one step by cathodic reduction of benzotrichloride in the presence of ketones (Table 1). The main by-product of the reaction is benzylidene dichloride, the amount of which can, however, be reduced by addition of sodium hydride.

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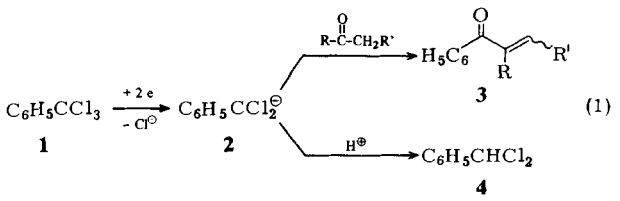


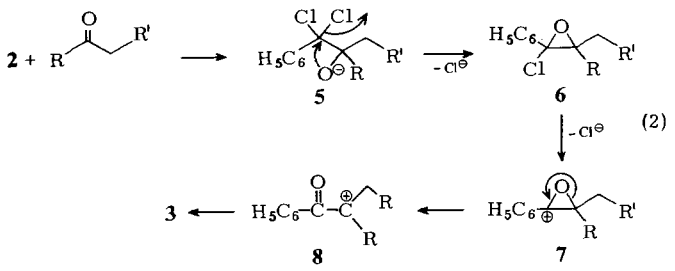
(1)

Table 1. (Selected data). Cathodic addition of benzotrichloride to ketones.

Ketone [a]	Products [b]	Yield [%] [c] 3	4
2-Butanone	2-Ethyl-1-phenyl-2-propen-1-one (40) (*E,Z*)-2-Methyl-1-phenyl-2-buten-1-one (60)	(48)	(40)
3-Methyl-2-butanone	2-Isopropyl-1-phenyl-2-propen-1-one (70) 2,3-Dimethyl-1-phenyl-2-buten-1-one (30)	59	16
3-Pentanone	(*E,Z*)-2-Ethyl-1-phenyl-2-buten-1-one	65 (34)	23 (59)
Acetophenone	1,2-Diphenyl-2-propen-1-one	58 (28)	29 (56)
Cyclopentanone	1-Cyclopentenyl phenyl ketone	64 (38)	22 (58)

[a] A solution of **1** (5–10 mmol) and ketone (10–20 mmol) in 50–70 mL of catholyte (0.5 M $LiClO_4$/tetrahydrofuran) is electrolyzed at 0 °C and −0.8 V (against Marple electrode) in a divided cell (cathode: Hg; anode Pt; diaphragm: G4 frit; anolyte: 0.2 M $LiClO_4$/dimethylformamide) until 100% conversion. [b] Characterized by elemental analysis and spectroscopic data; relative yields in brackets. [c] Current yield of isolated product with sodium hydride in the electrolyte (numbers in brackets without sodium hydride); **3** and **4** constitute 70–93% of the products.

The following reaction path seems plausible (eq. 2):



(2)

Reductive cleavage of **1** affords the anion **2**, which adds to the ketone to give **5**. The adduct cyclizes to the oxirane **6**, whose heterolysis leads to the intermediate cation **7**, which rearranges to **8**[5]. Subsequent deprotonation of **8** furnishes **3**. Benzylidene dichloride **4** may be formed by protonation of **2**, partly by H^+ ions from the anode compartment. An indication of **8** being formed as intermediate is afforded by the adducts obtained with norcamphor.

Table 3 (Selected data). Cathodic addition of benzotrichloride to methyl vinyl ketone and aldehydes.

Carbonyl compound [a]	Products (yield [%] [b])	Current yield of **4** [%]
Methyl vinyl-ketone	1,1-Dichlor-2-methyl-1-phenyl-3-buten-2-ol (12), *cis,trans*-2-Acetyl-1-chlor-1-phenylcyclopropane (24)	8
Pentanal	1,1-Dichlor-1-phenyl-2-hexanol (24), 1-Benzoyl-1-chlorpentane (23)	9
Isobutyr-aldehyde	1-Chlor-2-isopropyl-1-phenyloxirane (48) [e]	8

[a] Analogous to [a] in Table 1. [b] Current yield of isolated product. [e] Conversion into 1-benzoyl-1-chloro-2-methylpropane (15%) and 1-benzoyl-2-methyl-1-propanol (33%) on column filtration.

With methyl vinyl ketone and aldehydes, the reaction already terminates at **5** or **6** (Table 3).

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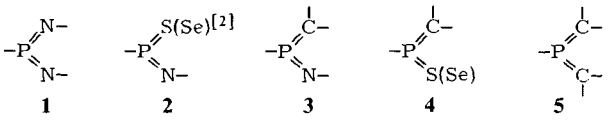
The First Bis(methylene)phosphoranes of Type R—P[=C(SiMe$_3$)$_2$]$_2$ with Tricoordinated Pentavalent Phosphorus**

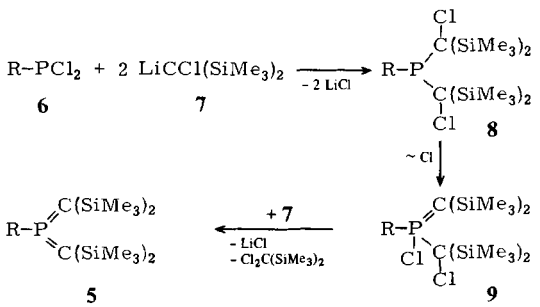
By *Rolf Appel**, *Johannes Peters*, and *Axel Westerhaus*

Dedicated to Professor Heinrich Puff on the occasion of his 60th birthday

In the search for unusual coordination numbers and novel bonding states of the phosphorus atom, stable phospha-alkenes, -alkynes[1] and three-coordinated phosphoranes of type **1–4**[2] have been found. Until now, attempts to synthesize the missing structural type **5** by oxidative addition of diazoalkenes to methylenephosphanes led only to the isomeric (PC_2)-phosphirane three-membered ring[3].

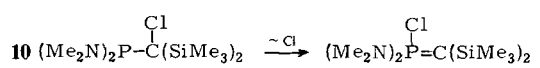


We have now been able to synthesize the compounds **5a–5c** for the first time by reaction of the lithiated chlorobis(silyl)methane **7** with the dichlorophosphanes **6a–6c**. Presumably the reaction proceeds according to Scheme 1.



Scheme 1.

The surprising 1,2 (C→P) chlorine migration **8**→**9** could be confirmed[4a] with model compound **10**, prepared from $(Me_2N)_2PCl$ and **7**.



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The bisylides **5a–5c** can be purified by vacuum distillation. They distill as red oils, which crystallize as yellow crystals. Their constitutions are confirmed by correct elemental analyses, molecular weight determinations, NMR spectra[5], and for **5c**, which is chiral in the crystal, by X-ray structure analysis[4b].

The formation and surprising stability of the novel bisylides **5** can be explained by the combination of kinetically controlled chlorotropy with 1,2-dechlorination and stabilisation by tetrasilylation of both carbanoid centers.

Procedure

56.6 mL of a commercial 1.6 M solution of *n*BuLi in hexane (87 mmol) is slowly dropped at −110 °C into a mixture of 200 mL of tetrahydrofuran (THF), 20 mL of diethylether, 20 mL of *n*-pentane, and dichlorobis(trimethylsilyl)methane (20 g, 87 mmol). The mixture is stirred for 3 h and a solution of **6** (29 mmol) in 20 mL of THF is slowly added. After warming up to room temperature overnight, the volatile fraction is removed *in vacuo*. The residue is taken up in 20 mL of *n*-pentane, filtered, and fractionated by distillation at 0.001 torr [**5a**: 131 °C, **5b**: 136 °C, **5c**: 118 °C]; yield 65–70%.

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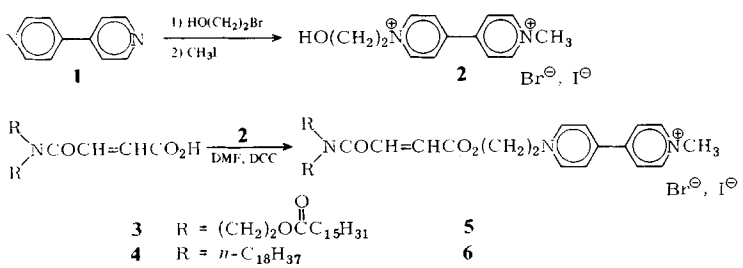
[5] Selected NMR-parameters (δ-values, J(P=C), in $CDCl_3$, room-temperature). $^{31}P\{^1H\}$-NMR (H_3PO_4 ext.): **5a**: +198, **5b**: +174, **5c**: +167, $^{13}C\{^1H\}$-NMR (TMS int.): **5a**: +81.6 (d, J=38.2 Hz), **5b**: +80.2 (d, J=46.8 Hz), **5c**: +55.6 (d, J=71.3 Hz).

Chemically Dissymmetrical, Polymerized Surfactant Vesicles: Synthesis and Possible Utilization in Artificial Photosynthesis**

By *Pietro Tundo, Kazue Kurihara, Donald J. Kippenberger, Mario Politi,* and *Janos H. Fendler**

The present communication reports the synthesis of the first chemically dissymmetrical[1a], redox-active[1b], polymeric[2] surfactant vesicles.



3 R = $(CH_2)_2OCC_{15}H_{31}$ (O) **5**

4 R = n-$C_{18}H_{37}$ **6**

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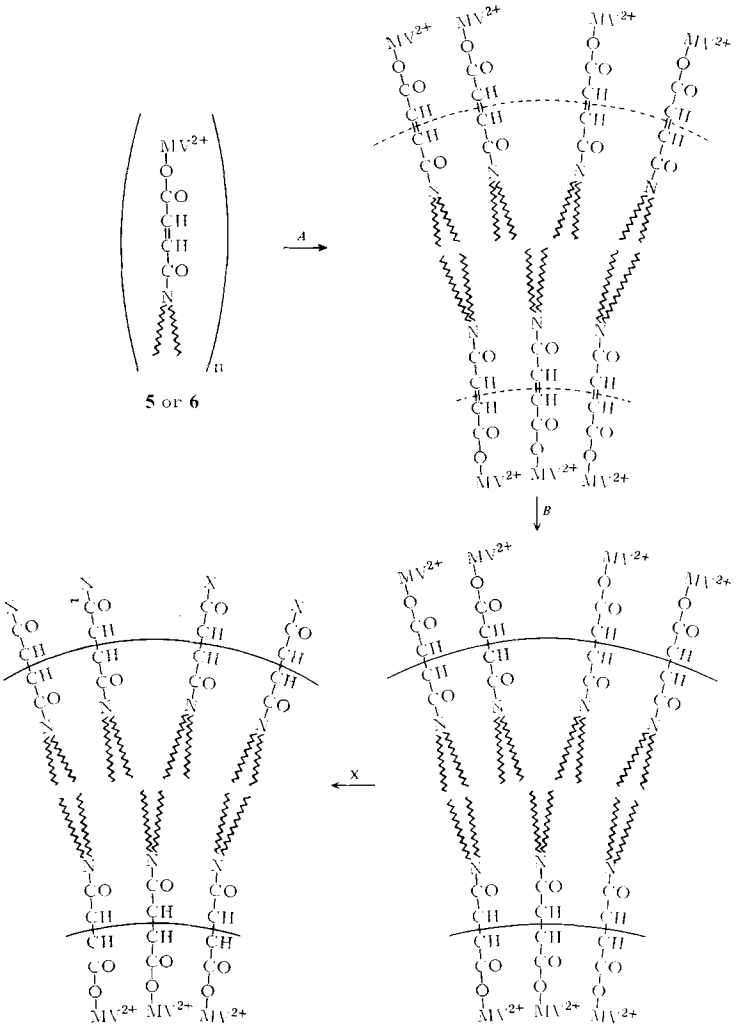
The vesicles, formed by sonication of **5** and **6**, have been characterized by electron microscopy, ^{1}H-NMR spectroscopy, and substrate entrapment[3]. Polymerization of the vesicles by azoisobutyronitrile (AIBN) or by irradiation occured slowly. Efficient copolymerization could be carried out, however, by adding acrylonitrile. Polymerization was followed by studying the disappearance of vinyl protons in the surfactants and in acrylonitrile by ^{1}H-NMR spectroscopy (200 MHz). Copolymerized vesicles remain stable in 25% EtOH.

Chemically dissymmetrical vesicles were prepared by reacting copolymerized vesicles with iminodiethanol (X in Scheme 1):



Scheme 1. X = iminoethanol; A = sonication; B = polymerization or copolymerization.

Photoexcitation of tris(2,2′-bipyridine)ruthenium perchlorate placed on the outside of the dissymmetrical vesicles **5** resulted in electron transfer from $Ru(bpy)_3^{2+}$ across the bilayers to give the long-lived reduced form of methyl viologen ($MV^{\oplus}$)[4]. This result is of interest in relation to the photosynthetic-analogous conversion of energy[5].

Procedure

2: **1** (25 mmol) was reacted with 2-bromoethanol (10 mmol) in 60 mL dimethylformamide (DMF) at 85 °C for 12 h. The insoluble disubstituted derivative was filtered off and the filtrate treated with diethyl ether, leading to the monoalkylated bipyridinium bromide in 77% yield

(m.p. = 195–197 °C, EtOH/Et_2O); 10 mmol in 50 mL DMF was added to a large excess of CH_3I; after 12 h at room temperature diethyl ether was added and the orange solid **2** filtered off; yield 92% (m.p. > 200 °C, MeOH).

5 and **6**: **3** (or **4**) (4 mmol) and **2** (3 mmol) in 10 mL of DMF and 5 mL of $CHCl_3$ were stirred for 12 h at 40 °C in the presence of 4.5 mmol of *N,N'*-dicyclohexylcarbodiimide (DCC). After cooling, the reaction mixture was filtered and **5** (or **6**) recovered by crystallization from MeOH. Yield: 40% **5**, 45% **6**; m.p. = 190 °C (decomp.) **5**; 180 °C (decomp.) **6**. All compounds gave correct ^{1}H-NMR spectra.

Vesicles: Chemically dissymmetrical vesicles were prepared as follows. 25 mg of **5** (or **6**), 3.6 mg of acrylonitrile, and 0.4 mg of AIBN (1 : 3 : 0.1) in 3 mL of water are sonicated for 9 min, and heated at 80 °C for 20 h. 68 mL of a 0.5 N aqueous solution of iminodiethanol (1.5 equiv.) was added. After 2.5 h at room temperature the solution was gel filtered on Sephadex (20–80 μ). Removal of viologen groups from the outer vesicle surface was demonstrated by the dithionite test[1b].

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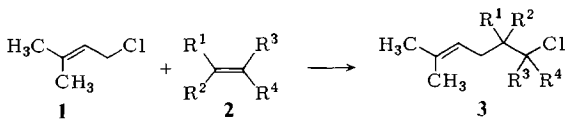
Cationic Prenylation of Olefins**

By *Herbert Klein, Anne Erbe,* and *Herbert Mayr**

Incorporation of the prenyl (3-methyl-2-butenyl) group into monoterpenes should provide an attractive synthetic route to sesquiterpenes. Previously, we have demonstrated[3] that Lewis acid catalyzed additions of alkyl halides to olefins may yield 1 : 1 addition products if the products solvolyze more slowly than the starting alkyl halides; otherwise, the alkyl halides are only converted to a small extent and polymerization of the alkenes takes place.

In this communication we report some consequences of this rule for the cationic prenylation of alkenes **2**, which are considered models for monoterpenes.



When prenyl chloride **1** is added dropwise to solutions of **2a–2j** and $ZnCl_2/Et_2O$ in CH_2Cl_2[4] at −78 °C, the 1 : 1 products **3a–3j** are obtained in moderate to good yields (Table 1). Both **2k** and ethyl vinyl ether **2l** polymerize under these reaction conditions, even if their concentration is kept small by simultaneous dropwise addition of the reactants to the catalyst solution. The ^{13}C-NMR spectra of the 1 : 1 products show that the addition reactions generally take place in a Markovnikov sense and that the prenyl cation is attacked almost exclusively at the CH_2 group.

Table 1. $ZnCl_2/Et_2O$ catalyzed additions of prenyl chloride to olefins **2**.

	Olefins **2**	Yield of **3** [%]
a	$H_2C{=}CHCH_3$	32 [a]
b	$H_2C{=}C(CH_3)_2$	65
c	$H_2C{=}C(CH_3)C_2H_5$	67
d	methylenecyclopentane	73
e	$H_2C{=}C(CH_3)CH(CH_3)_2$	61 [b]
f	$H_2C{=}C(CH_3)C(CH_3)_3$	66
g	$CH_3{-}CH{=}C(CH_3)_2$	78 [b]
h	1-methylcyclohexene	85 [b, c]
i	$(CH_3)_2C{=}C(CH_3)_2$	76
j	$H_2C{=}CHPh$	75
k	$H_2C{=}C(CH_3)Ph$	—
l	$H_2C{=}CHOC_2H_5$	—

[a] $C_xH_{15}Cl$-isomeric mixture. [b] Apart from *ca.* 10% hydride shift product. [c] *cis-trans*-Mixture.

The different behavior of **2a–2j** and of **2k** and **2l** can be rationalized by considering the relative solvolysis rates[7] of educts and products. Olefins **2a–2j** yield secondary and tertiary alkyl chlorides, respectively, which dissociate more slowly than **1**: the addition reactions, therefore, terminate at the 1 : 1 stage. On the other hand, **2l** and **2k** give dialkylphenylcarbinyl chlorides and α-chloro ethers, respectively. Because of their high dissociation rates, these intermediate products react faster with olefins than with **1**, thus leading to polymers.

In the reaction of **1** with propene **2a** only a relatively small yield of 1 : 1 products is isolated, although here the biggest difference in solvolysis rates between educt and product exists. Adducts **3** are not only potential alkylating agents, but can also be electrophilically attacked at the trisubstituted double bond by prenyl cations. This side reaction can usually be suppressed by using a three-to five-fold molar excess of olefin. For example, the yield of **3g** increases from 47 to 78% when **1** is added to **2g** in the molar ratio 1 : 4 instead of 1 : 1; the difference between the dissociation rates of **1** and **3g** is obviously sufficient to prevent reaction of **3g** with the excess olefin **2g**. Since the double bond of **3a** is considerably more nucleophilic than the double bond of propene **2a**, we only obtained a moderate yield of 1 : 1-product even when a ten-fold excess of propene was used.

These results demonstrate that problems arise with Lewis acid catalyzed additions of prenyl chloride to olefins of high and of low nucleophilicity; in one case electrophilic, and in the other case nucleophilic sequence reactions take place. 1,1-Dialkyl-, trialkyl-, and tetraalkylethylenes, simple analogues of many terpenes, however, possess intermediate nucleophilicity and can be monoprenylated in good yields.

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

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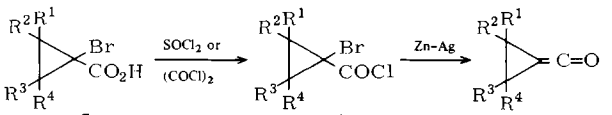
[7] k_1 of $PhC(CH_3)_2Cl$ in 80% aqueous EtOH at 25 °C ≈ 0.02 s^{-1}; for solvolysis constants of other model compounds: ref. [3].

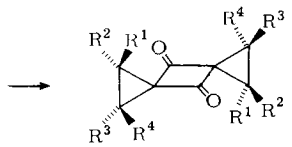
Carbonylcyclopropanes (Cyclopropylidenemethanones): Preparation and Steric Course of Cyclodimerization to Dispiro[2.1.2.1]octane-4,8-diones**

By *H. M. R. Hoffmann*, Jan Michael Wulff, Angela Kütz,* and *Rudolf Wartchow*

Substituted carbonylcyclopropane derivatives (cyclopropylidenemethanones) and their dimers have hitherto not been described, although the parent compounds **7a** and **8a** are known[1]. However, **7a** cannot be obtained on a preparative scale and derivatives of **7a** are not accessible[1,2]. Furthermore, dehydrochlorination of cyclopropanecarboxylic acid chloride with tertiary amines was not successful. Since a well-known approach to ketenes involves metal-induced dehalogenation of 2-halogenocarboxylic acid halides[5], we synthesized the 1-bromocyclopropanecarboxylic acids **5b—5d** as described by *Köbrich*[6]. Conversion of **5b—5d** into 1-bromocyclopropanecarboxylic acid chlorides **6b—6d** followed by dehalogenation with Zn/Ag[7] gave, after aqueous work-up, alkylated dispiro[2.1.2.1]octane-4,8-diones **8b—8d** as major products and, interestingly, some cyclic trimers.

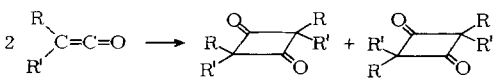


5 6 7



8a, $R^1 = R^2 = R^3 = R^4 = H$
8b, $R^1 = R^2 = H$; $R^3 = R^4 = Me$
8c, $R^1 = R^2 = R^3 = R^4 = Me$
8d, $R^1 = R^4 = H$; $R^2 R^3 = (CH_2)_4$

The structures of the colorless, crystalline cyclodimers **8b—8d** were secured spectroscopically; **8c** shows only one signal in the ^{1}H-NMR. spectrum ($\delta = 1.39$), and three singlets and one quartet in the ^{13}C-NMR spectrum. Hitherto, there have been no attempts to study the steric course of cyclodimerization of ketenes[5]. *A priori*, two isomeric cyclobutane-1,3-diones, the *syn*-dimer **10** and the *anti*-dimer **11** can be formed.



9 10 11

X-Ray crystal structure analysis (Fig. 1) shows that **7d** cyclodimerizes to the less encumbered *anti*-dimer **8d**, in which the two cyclohexane moieties are *trans* to each other. It is worthy of note that the cyclodimerization of **7b** to **8b** is again stereoselective (≥95%), and we assume that the *anti*-dimer **8b** is also formed preferentially in this reaction.

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[**] This work has been presented in part at the Int. Symp. Chem. of Carbocations in Bangor, Wales, September 7—11, 1981. We thank the Fonds der Chemischen Industrie for financial support.

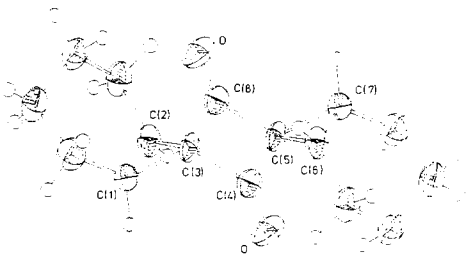

Figure 1. Structure of **8d** in the crystal.

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Angew. Chem. Suppl. 1982, 17

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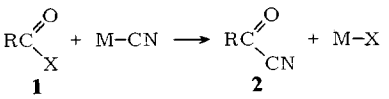
Synthesis of Acyl Cyanides from Acyl Iodides**

By *Klaus Haase* and *H. M. R. Hoffmann**

Acyl cyanides (α-ketonitriles) **2** are versatile synthetic intermediates[1], and are generally prepared by the reaction of carboxylic acid chlorides, carboxylic acid bromides, and occasionally carboxylic acid anhydrides with a variety of metal cyanides[1].



1 **2**

R = Alkyl, Aryl; X = Cl, Br, I, OCOR;
M = Na, Cu, Tl, Me_3Si, Bu_3Sn, H

We now report that acyl cyanides **2** can be prepared conveniently using the very reactive acyl iodides **1** (X = I)[2] and CuCN (Table 1). Two solvents, *i.e.* dichloromethane (method A) and acetonitrile (method B), were employed. While CuCN is partially soluble in CH_3CN, CH_2Cl_2 can be removed more easily on work-up of the reaction mixture. *Inter alia* we have successfully synthesized 2-oxo-3-phenylpropanenitrile **2e**, which cannot be

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[**] Reactive Iodine Compounds, Part 2. This work has been presented in part at the International Symposium on the Chemistry of Carbocations in Bangor, North Wales, Sept. 7—11, 1981. We thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for financial support.—Part 1: [2].

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Table 1. Acyl cyanides **2** from acyl iodides **1** and CuCN.

2, R	Method	Yield [%] [a]	Ref. Yield [%]
a n-C_7H_{15}	B	78	-
b [b]	B	51	85 [c]
	A	70	
c PhCH=CH	B	53	59 [4]
d $(CH_2)_2CH$	B	27	82 [1c]
	A	61	38 [4]
e $PhCH_2$	B	49	-
	A	61	-

[a] Yields were not optimized. [b] 2,7-Dioxo-octanedinitrile. [c] Crude yield; F. Asinger, A. Saus, H. Offermanns, H. D. Hahn, *Justus Liebigs Ann. Chem. 691* (1966) 92.

prepared by the convential procedure[1c]. Similarly, α,β-unsaturated acyl cyanides such as 3,4-dimethyl-2-oxo-3-pentenenitrile have been obtained[3]; hereby, the olefinic double bond tends to shift out of conjugation under more forcing conditions.

Acyl cyanides **2** can also be rapidly prepared under mild conditions in a one-pot procedure starting from acyl chlorides, CuCN, and iodide ion[3].

Experimental Procedure

All reactions are carried out under an atmosphere of N_2, because acyl iodides **1** (X = I) are easily oxidized.

Method A: **2d:** CuCN (1.2 g, 13 mmol) was gently refluxed in CH_2Cl_2 (15 mL) and **1d** (1.4 g, 7.1 mmol) added in one batch. After being refluxed for 1–2 h, the mixture was filtered from CuI, and CH_2Cl_2 was removed at 0–5 °C. Kugelrohr distillation gave **2d** (420 mg, 62%)[4].

Method B: **2e:** A suspension of CuCN (1.2 g, 13 mmol) in anhydrous acetonitrile (100 mL) was warmed to 40–60 °C and **1e**[2] (2.5 g, 10 mmol) was added in one batch: after 2–3 min a yellow, almost clear solution resulted. The solution was stirred for 1 h, and the acetonitrile was removed using a rotary evaporator. The product was dissolved in CH_2Cl_2 and CuI filtered off. After evaporation of CH_2Cl_2 the residue was distilled twice (Kugelrohr, b.p. 100–120 °C/3 torr) giving pure **2e** (730 mg, 50%)[5].

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[5] **2e:** IR (CCl_4) 2220 (m), 1720 (vs), 1495 (m), 1455 (m), 1210 (m), 1055 (s), 715 (s) cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ = 4.0 (s, 2H), 7.3–7.5 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ = 50.8 (C-3), 113.1 (C-1), 128.6, 129.1, 129.2, 130.0 (aromat.), 174.4 (C-2).

BOOK REVIEWS

Nucleotide Analogs. Synthesis and Biological Function. By *K. H. Scheit.* John Wiley & Sons, New York 1980. xi, 288 pp., price £ 16.00.

The importance of nucleotides in biological processes has led to intense preoccupation with this class of natural substances. The base, sugar and phosphate portions are modified for a variety of purposes. One reason for the synthesis of nucleotide analogs is doubtless to use them in obtaining information about nucleotide metabolism and about the expression and replication of genetic information. Another driving force is the hope that once the mechanisms of expression and replication are known, nucleotide analogs may be designed for general use as chemotherapeutics, for example as interferon inducers or antiviral agents. A wealth of literature difficult to grasp other than by a specialist has been devoted to this theme, which has been studied for many years and is still growing today. This book fills a gap in this respect, since apart from an introduction to the subject, it presents an up-to-date review of the synthesis and properties of nucleotide analogs, taking into account the structure-function relationships. Nucleotides are described that are modified on or in the heterocycle, together with others with unusual *N*-glycosyl bonds and altered sugar radicals. Moreover, the book gives an account of the newer methods of synthesizing phosphate esters, nucleotide polyphosphates and nucleotides with modified phosphate radicals. The final chapter deals with the synthesis of chemically reactive and photoreactive derivatives, *e.g.* for use in affinity labeling and affinity chromatography. Ample references at the end of each chapter constitute an introduction to the primary literature. The many summary formula illustrations facilitate the reading of the text. Thus, a study of this book should be profitable both for those new to the field and for those who have been involved in it for years. For the first of these, it is a modern introduction, and for the latter, an up-to-date summary from which they should certainly derive stimulus for their own research.

Hubert Köster [NB 553 IE]

Ullmanns Encyklopädie der technischen Chemie. Edited by *E. Bartholomé, E. Biekert, H. Hellmann, H. Ley* (deceased), *W. M. Wiegert* (deceased), *and E. Weise.* Vol. 19: Polyacryl-Verbindungen bis Quecksilber. Verlag Chemie, Weinheim 1980. 4th Edition, xvi, 672 pp., bound, DM 525.00.

This 19th volume of Ullmann's Encyclopedia[*] deals mostly with the polymers, which occupy over half of the volume; if the biopolymers are included (proteins with 67 pp., and polysaccharides, with 31 pp.), this rises to two-

[*] See *Angew. Chem. 92* (1980) 866; *Angew. Chem. Int. Ed. Engl. 19* (1980) 838.

thirds. There are two other classes of biopolymers, namely cellulose and starches, that are not only dealt with in this volume, but appear as cross-references to other volumes. Further articles in this volume relate to organic intermediate products (*e.g.* Propanediol, 8 pp.; Propionic acid and its derivatives, 9 pp.; Propylene, 8 pp.; Propylene oxide, 11 pp.; Propanol, 9 pp.; Propanolamine, 11 pp.; Pyridine and its derivatives, 27 pp.), to pharmaceuticals and their pre-products (Prostaglandins, 8 pp.; Purine and its derivatives, 5 pp.; Pyrazolone, 8 pp.; Pyrimidine and its derivatives, 3 pp.), to inorganic chemistry (Mercury, 29 pp.; Porcelain, 20 pp.), and to applied technologies (Pelleting compounds, 14 pp.; Powder metallurgy, 14 pp.; Pyrotechnics, 16 pp.). Of the polymers themselves, the polyolefins take up the most space with 60 pp., corresponding to their importance, followed by the polyurethanes with 41 pp., polystyrene including its copolymers with 31 pp., polyacrylates and polymethacrylates with 30 pp., and finally the polyesters with 28 pp. Under these entries for the individual classes of polymers, essentially only the manufacture and the chemical properties are dealt with, while anything to do with the application of the polymers is to be found under other entries, mainly in Volume 15 under Plastics or under special entries, for example Fibers, in which, *inter alia*, the application of polyesters as chemical fibers is dealt with. Special mention should also be made of the entry on Polymerization techniques (59 pp.), which gives a summary treatment of polymerization processes such as solution, suspension and emulsion polymerization. This review of an aspect of the technical production of polymers that is becoming increasingly important, fills a long-standing gap in this area, and raises the question whether it might not be worthwhile to expand this entry, in due course, into a monograph. It should also be mentioned that the entry on Proteins also gives an account of modern methods for the biotechnological preparation of individual proteins on the basis of unconventional carbon sources (ethanol, alkanes). Finally, it only remains to be said that this volume maintains the familiar high quality of Ullmann's Encyclopedia, which should be available in any chemical library on account of its information content.

Ulfert Onken [NB 555 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 (Federal Republic of Germany).

The Flavobacterium-Cytophaga Group. Edited by *H. Reichenbach* and *O. B. Weeks*. GBF Monograph Series, No. 5. Verlag Chemie, Weinheim 1981. xiii, 217 pp., bound, DM 88.00.—ISBN 3-527-25919-8

Transition Metal Chemistry. Current Problems of General, Biological and Catalytical Relevance. Edited by *A. Müller* and *E. Diemann*. Verlag Chemie, Weinheim 1981. xii, 338 pp., bound, DM 88.00.—ISBN 3-527-25910-4

Water Pollution Research and Development. Part 1—4. Executive Editor: *S. H. Jenkins*. Pergamon Press, New York 1981. xii, 1388 pp., bound, $ 195.00.—ISBN 0-08-026025-X

Two-phase Flows in Chemical Engineering. By *D. Azbel*. Cambridge University Press, Cambridge 1981. xx, 311 pp., bound, £ 45.00.—ISBN 0-521-23772-6

Bindung und Struktur. Schülerheft und Lösungsheft. By *M. Tausch*. Verlag Ferdinand Schöningh, Paderborn 1981. Schülerheft: 143 pp., bound, DM 14.20; Lösungsheft: 18 pp., bound, DM 2.80.—ISBN 3-506-13901-0 bzw. 3-506-13902-9

Analytikum—Methoden der analytischen Chemie und ihre theoretischen Grundlagen. By *K. Doerffel* and *R. Geyer*. VEB Deutscher Verlag für Grundstoffindustrie, Leipzig 1981. 5th Edit. 615 pp., bound, DM 60.00

Carl Duisberg. Eine Biographie. By *H.-J. Flechtner*. Econ Verlag, Düsseldorf 1981. 432 pp., bound, DM 12.80.—ISBN 3-430-12809-9

Advances in Polymer Science. Vol. 40. Luminescence. With contributions by *E. V. Anufrieva, K. P. Ghiggino, Yu. Ya. Gotlib, D. Phillips*, and *A. J. Roberts*. Springer-Verlag, Berlin 1981. v, 174 pp., bound, DM 82.00.—ISBN 3-540-10550-6

NMR. Vol. 19. NMR in Medicine. Edited by *R. Damadian*. Springer-Verlag, Berlin 1981. v, 174 pp., bound, DM 98.00.—ISBN 3-540-10460-7

Catalysis—Science and Technology. Vol. 1. Edited by *J. R. Anderson* and *M. Boudart*. Springer-Verlag, Berlin 1981. x, 309 pp., bound, DM 142.00.—ISBN 3-540-10353-8

Lagerstätten der Steine, Erden und Industriemineralien. Untersuchung und Bewertung (Vademecum 2). Published under the auspices of Gesellschaft Deutscher Metallhütten- und Bergleute (GDMB). Verlag Chemie, Weinheim 1981. xii, 248 pp., bound, DM 69.00.—ISBN 3-527-25923-6

Catalysis and Chemical Processes. Edited by *R. Pearce* and *W. R. Patterson*. The Blackie Publishing Group, Glasgow 1981. xix, 348 pp., bound, £ 25.00.—ISBN 0-249-44160-8

Atmospheric Aerosol: Source/Air Quality Relationships. ACS Symposium Series No. 167. Edited by *E. S. Macias* and *P. K. Hopke*. American Chemical Society, Washington 1981. 359 pp., bound, $ 39.75.—ISBN 0-8412-0646-5

13. Spektrometertagung. Düsseldorf, 29. 9. through 1. 10. 1980. Edited by *K.-H. Koch* and *H. Massmann*. Walter de Gruyter, Berlin 1981. xvi, 426 pp., bound, DM 140.00.—ISBN 3-11-008456-2

Reaktionen und Synthesen im organisch-chemischen Praktikum. By *L.-F. Tietze* and *T. Eicher*. Thieme Verlag, Stuttgart 1981. xxxii, 592 pp., bound, DM 54.00.—ISBN 3-13-612301-8

Die Zelle. Struktur und Funktion. Edited by *H. Metzner.* Wissenschaftliche Verlagsgesellschaft, Stuttgart 1980. 3rd completely revised edition. x, 612 pp., bound, DM 96.00.—ISBN 3-8047-0607-X

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Insights into Chemical Engineering. (Selected Papers of P. V. Danckwerts). By *P. V. Danckwerts.* Pergamon Press, New York 1981. xviii, 307 pp., bound, $ 65.00.—ISBN 0-08-026250-3

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Steroid Analysis by HPLC. Recent Applications. Vol. 16. Edited by *M. P. Kautsky.* Marcel Dekker, Basel 1981. xii, 397 pp., bound, SFr. 135.00.—ISBN 0-8247-1324-9

Hummel/Scholl. Atlas der Polymer- und Kunststoffanalyse. Band 3: Zusatzstoffe und Verarbeitungshilfsmittel. By *F. Scholl.* Carl Hanser Verlag, München and Verlag Chemie, Weinheim 1981. 2nd completely revised edition. xxiv, 696 pp., 1355 spectra bound, DM 520.00 (subscription price when ordering all volumes DM 450.00).—ISBN 3-446-12564-7 bzw. ISBN 3-527-25799-3

Lehrwerk Chemie—Einführung in die Laboratoriumspraxis. Arbeitsbuch O. Von einem Autorenkollektiv. VEB Deutscher Verlag für Grundstoffindustrie, Leipzig 1981. 2nd edit. 296 pp., bound, *ca.* DM 30.00

Verfahrenstechnik in Chemieberufen. Berufsschullehrbuch. By *R. Kalthofen, G. Eckert, V. Mede,* and *H. Thomas.* VEB Deutscher Verlag für Grundstoffindustrie, Leipzig 1981. *ca.* DM 23.00.

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Lasers in Chemical Analysis. Edited by G. M. Hieftje, J. C. Travis, and *F. E. Lytle.* The Humana Press, Clifton 1981. xiii, 310 pp., bound, £ 29.00.—ISBN 0-89603-027-X

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Three Concepts of Time. By *K. G. Denbigh.* Springer-Verlag, Berlin 1981. viii, 180 pp., bound, DM 39.00.—ISBN 3-540-10757-6

Biologie. Eine Vorlesungsreihe für Mediziner und Naturwissenschaftler. Edited by *D. Starck, K. Fiedler, P. Harth,* and *J. Richter.* Verlag Chemie, Weinheim 1981. xxxi, 1118 pp., bound, DM 88.00.—ISBN 3-527-25821-3

The ^{18}O-Exchange Method in Zeolite Chemistry. Synthesis, Characterization and Dealumination of High Silica Zeolites. By *R. von Ballmoos.* Salle + Sauerländer, Frankfurt 1981. viii, 235 pp., bound, DM 45.00.—ISBN 3-7935-5523-2

Corrigendum

The following corrections should be made to the short communication entitled, "Di-*tert*-butylthia- and -selenadiphosphirane" by Marianne Baudler, Horst Suchomel, Gabriele Fürstenberg, and Ulrike Schings, *Angew. Chem. Int. Ed. Engl. 20* (1981) 1044:

On p. 1045, left-hand column:
"... $(t\mathrm{BuP})_2\mathrm{SiPh}_1$[1](1 : 1 : 1), ..."
in line 13 should read:
"... $(t\mathrm{BuP})_2\mathrm{SiPh}_2$[1](1 : 1 : 1) ..."

On the same page, same column: "...; but *tert*-butyl groups ..." in line 49 should read: "...; but **the** *tert*-butyl groups ...".

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The Norbornyl Cation: Prototype of a 1,3-Bridged Carbocation

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The protracted discussion of whether 2-norbornyl cations are bridged or unbridged, *i.e.* nonclassical or classical, has lost most of its meaning, because these terms apply to the extremes of a graded series of structures. This is shown by a study of the solvolysis of stereoisomeric 6-substituted 2-norbornyl toluenesulfonates. Norbornyl and other bicyclic cations, to which nucleophiles have limited access, are stabilized by bridging between the cationic center and a saturated carbon atom in the β-position. Bridging is reduced by electron-attracting substituents and by bridging.

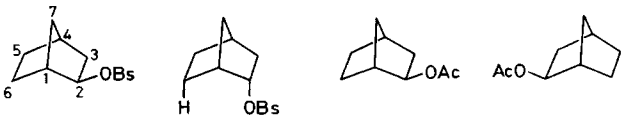
1. Introduction

During the past three decades numerous chemists have been engaged in attempts to elucidate the structure of the 2-norbornyl cation. Despite these efforts a stalemate rather than an agreement has been reached[**], the reiteration of the same positions having largely replaced the quest for new solutions. This development is deplorable, in that the issue is not relevant to norbornyl cations alone, but applies to the structure of carbocations in general, *i.e.* to important intermediates in organic and bioorganic processes. The experimental results described in the following article, although they partly confirm present hypotheses, open up fresh perspectives. The following summary of current views should help in understanding the nature of the problem.

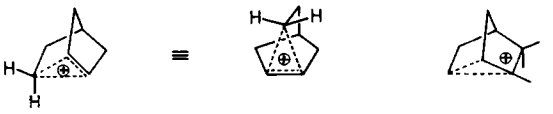
2. The Problem

Thirty years ago *Winstein* and *Trifan*[3] reported the surprising results of their investigation of the reactions of optically active 2-*exo*- and 2-*endo*-norbornyl *p*-bromobenzenesulfonates, *i.e.* the "brosylates" **1** and **2**, in acetic acid. In these "acetolyses" the *exo*-brosylate **1** reacted 350 times faster than the *endo*-epimer **2**. Since the 2-*exo*-acetate **3** was obtained almost exclusively in both cases the *exo*-brosylate had evidently undergone substitution at C2 with retention, the *endo*-brosylate with inversion of configuration at C2. Furthermore, while the acetate derived from **1** was completely racemized, and hence consisted of equal amounts of the enantiomers **3a** and **3b**, the acetate from **2** retained some optical activity.

Winstein postulated a common cause for the higher rate of the 2-*exo*-brosylate **1** and for its conversion to racemic *exo*-acetate **3**, namely anchimeric assistance to ionization



1 **2** **3a** **3b**



4 **4** **5**

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[**] Cf. the monograph by *H. C. Brown* with comments by *P. von R. Schleyer* [1], and the reviews by *G. D. Sargent.* [2a], *G. A. Olah* [2b], and *W. Kirmse* [2c].

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of the OBs group by the antiperiplanar C1—C6 bond[*] with formation of the symmetrically bridged cation **4**. It was reasoned that attack by acetic acid, or by other nucleophiles, should take place on the *exo*-side of the cation **4** only, because of shielding by the partial bonds between C6—C1 and C6—C2.

Furthermore, since the atoms C1, C2 and C3 are held together by two electrons only and since C6 is (untypically) pentacoordinate, the cation **4** was called "nonclassical", following a suggestion by *Roberts*[4]. In contrast to **4**, "classical" carbenium ions, such as **6**, are well represented by the usual two-electron (Lewis) bonds. *Winstein*'s formula for the cation **4** was not novel; indeed a similar "nonclassical" structure **5** had been proposed ten years earlier by *Wilson et al.*[5] to describe the intermediate in the camphene hydrochloride/isobornyl chloride rearrangement.

The 2-*endo*-brosylate **2** does not fulfill the stereoelectronic requirement for effective participation of the C1—C6 bond because the latter and the C2—OBs bond are not antiperiplanar. According to *Winstein* the brosylate **2** therefore reacts at a normal rate to form the "classical" carbenium ion **6a**. He assumed, however, that it was subsequently converted into the bridged cation **4** because the derived *exo*-acetate **3** was extensively racemized.

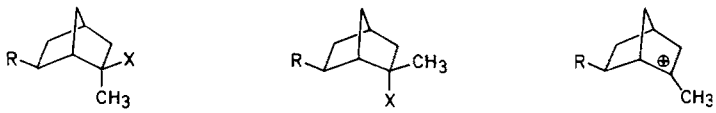
6a **6b** **6b**

Brown and others have shown since then that the norbornane molecule is preferentially attacked on the *exo*-side by numerous reagents[1]. Consequently, there no longer was a compelling reason to postulate a bridged cation **4** in order to rationalize the formation of the *exo*-acetate **3** from **1** and **2**. Indeed, if the unbridged cation **6a** underwent a rapid "degenerate" Wagner-Meerwein rearrangement[**] before being captured by solvent, racemic acetate **3** should also be produced. *Brown* attributed the 350-fold lower rate of the *endo*-brosylate **2** to sterically hindered departure of the OBs group due to the *endo*-H atom at C6 in the U-shaped structure. Furthermore, he assumed that the carbenium ions **6a** and **6b** were stabilized by inductive and hyperconjugative effects, which do not involve a significant change of molecular structure[1]. Since this time, the question "classical" or "nonclassical" has dominated the dispute about the norbornyl cation.

More recently *Jensen et al.*[6a] and *Traylor et al.*[6b] suggested an alternative explanation for the high k_t/k_2 ratio

7 **8**

based on hyperconjugation of the C1—C6 bond, which, in the 2-*exo*-brosylate **1**, is antiperiplanar with respect to the C2—OBs bond. In this way, part of the positive charge generated in the transition state **7** can be transferred to C6 without causing additional strain. But since the cation **8** derived from **1** possesses the same geometry as the unbridged cation **6**, the formation of racemic acetate **3** still requires a rapid and reversible rearrangement of **8** to its enantiomer. The rate of reaction of the *endo*-brosylate, however, was thought to be considerably reduced because the C1—C7 and the C2—OBs bonds are only approximately antiperiplanar and the delocalization of positive charge therefore less favorable.



9 **10** **11**

Many arguments have been advanced for and against these hypotheses[1]; however, there appears to be agreement that tertiary 2-norbornyl derivatives, such as **9** and **10** (R = H, X = *p*-$NO_2C_6H_4COO$) react *via* "classical" carbenium ions **11** and that the high *exo*/*endo* rate ratios, which are also observed in this series, are due to sterically hindered ionization of the 2-*endo*-nucleofuge X in **10**[1]. However, caution is also indicated here, as will be shown later.

The main problem, therefore, is how to explain high *exo*/*endo* rate ratios and how to describe the intermediate cations; *i.e.* are the unsymmetrical cations **6a** and **6b** energy minima on the energy hypersurface, and is the symmetrically bridged cation **4** the transition state for rearrangement, or does the cation **4** correspond to a single minimum of lower energy (cf. the unbroken curves in Fig. 1), as supporters of "nonclassical" carbocations assume.

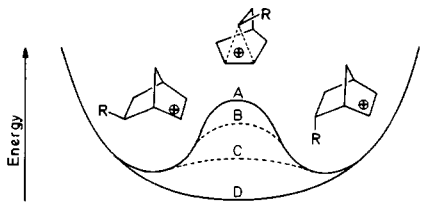


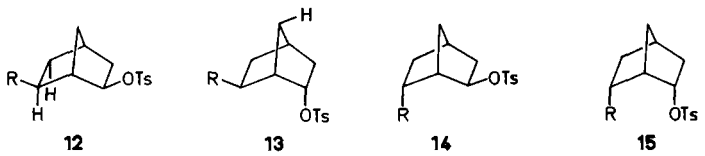
Fig. 1. Solvolysis of 6-substituted 2-norbornyl sulfonates Section from a plot of the potential energy *versus* the reaction coordinate. Full curves, A: double minima for two "classical" norbornyl cations **6**; D: Energy minimum for the hypothetical "nonclassical" cation **4**. Dotted curves B and C: Energy barriers (lowered due to 1,3-bridging) between the two energy minima corresponding to the classical norbornyl cations **6**.

Possibly, carbocations conform to a continuous range of intermediate, partially bridged structures, as recently proposed by *Olah* and *Schleyer et al.*[7]. It is also conceivable that the height of the energy barriers in Figure 1 is influenced by substituents. In fact, studies of this kind have been carried out with 1-substituted[8] and with some 5-substituted norbornyl derivatives[9]. For various reasons it appeared more promising to study the effect of substituents at C6 on the rates and products of 2-norbornyl *p*-toluene-

[*] The term "anchimeric" normally describes the participation of a neighboring nucleophilic substituent, such as R_2N, HO, $COO^{\ominus}$, RS or a π-bond, in the ionization step. In this case the use of the term is extended to include the participation of a C—C single bond, *i.e.* so-called σ-participation.

[**] That is, a rearrangement leading to the same structure and therefore not detectable by the usual means.

sulfonates (tosylates) in all their stereoisomeric variations, namely **12**, **13**, **14**, and **15**, including the tertiary 2,4-dinitrophenyl ethers **9** and **10** (X = 2,4-$(NO_2)_2C_6H_3O$)[*]. These



12 **13** **14** **15**

studies should reveal whether substituents at C6, including hydrogen, exert a polar, a steric or a stereoelectronic effect or, possibly, a combination of these.

3. Special Features of Norbornane Derivatives

In order to understand the unique reactivity of 2-norbornyl sulfonates some features peculiar to their bicyclic structure should be recognized. Thus, the latter has a strain energy of *ca.* 17 kcal/mol[13] due to the fixed boat conformation and the C1—C7—C4 bond angle of 94°[12]. Furthermore, rearside *exo*- and *endo*-attack at C2 is sterically hindered by the *endo* hydrogen atoms at C5 and C6 and by the *syn* hydrogen atom at C7, respectively, as shown in **12** and **13**, R = H. Therefore, these compounds do not react with strong nucleophiles such as KOH and C_6H_5SNa[14] by the bimolecular substitution mechanism (S_N2), nor with less nucleophilic solvents[15] in a k_s process[**]. In fact they react by the unimolecular (S_N1) substitution mechanism, *i.e.* by a k_c process[***]. Since the positive charge generated in the transition state cannot be directly transferred to the solvent, it must be delocalized internally by induction, hyperconjugation or fragmentation[***]. Degenerate rearrangements and hydride shifts[17], commonly observed with secondary norbornyl derivatives, are a further consequence of sterically hindered nucleophilic solvation.

4. Polar or Steric Substituent Effects in Secondary Norbornyl Tosylates

Our previous studies of the influence of substituents upon the solvolysis rates of saturated compounds have shown their inductive (I) effect to be dominant[18]. In these studies the difference between the pK_a values of quinuclidinium perchlorate **16** (R = H) and its 4-substituted derivatives served as a measure of the I-effect; additional factors, such as steric, mesomeric and hyperconjugative effects cannot be significant in these saturated salts. Inductive substituent constants σ_I^q were thus derived using the equation

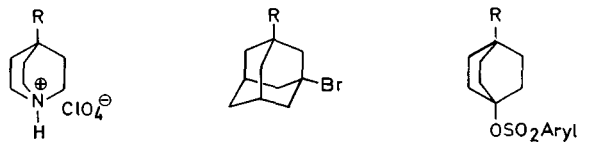
$$pK_a^H - pK_a^R = \rho\sigma_I^q \qquad [****]$$

in which the reaction constant ρ is unity by definition[19].

As follows from the Hammett-Taft relationship

$$\lg(k/k_0) = \rho\sigma_I^q$$

the logarithms of the rate constants ($\lg k$) for a series of substituted norbornyl tosylates should correlate linearly with the respective σ_I^q values if the rates are controlled by the I effect of the substituent only, as in the case of the pK_a values for the corresponding quinuclidines **16**. In addition, the reaction constant ρ measures the sensitivity of the rate to the polarity of the substituent. Thus, $\lg k$ for the unstrained 1-substituted 3-bromoadamantantes **17**[18b] and for the 4-substituted bicyclo[2.2.2]octyl sulfonates **18**[18d] correlate well with σ_I^q values, when R represents a neutral or a −I substituent, such as hydrogen, alkyl, halogen, $COOCH_3$ or NO_2. Clearly, these substituents control ionization rates by exerting their I effect.



16 **17** **18**

This applies also to the norbornyl tosylates **12** and **13** as shown by the plots in Figure 2. However, the reaction constant ρ of −2.0 for the *exo*-tosylates **12** is more than twice

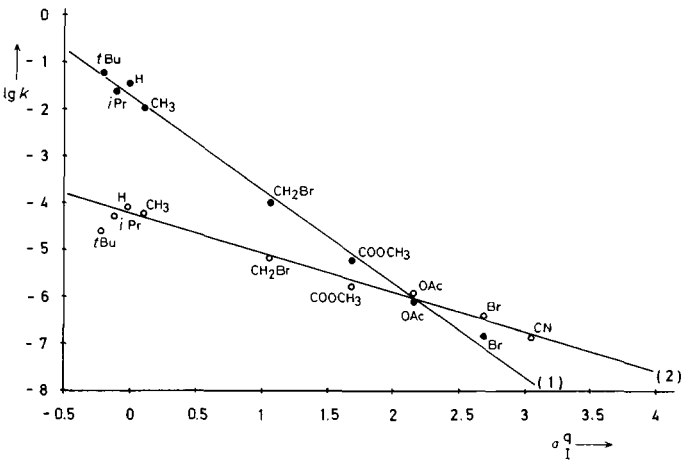


Fig. 2. Plots of lg *k* of the solvolysis of 6-*exo*-substituted 2-*exo*- (curve 1) and 2-*endo*-norbornyl tosylate (curve 2) **12** and **13**, respectively, against inductive substituent constants σ_I^q (80% ethanol, 70 °C).

as large as that of −0.86 for the *endo*-tosylates **13**. It follows that the I effect is transmitted far more strongly in the W-like conformation **12** than in the sickle-like conformation **13**[*]. Moreover, the correlation of $\lg k$ for **12** and **13** with the respective σ_I^q values eliminates the need to postulate an additional effect, such as CC-hyperconjugation (see Section 2). On the other hand, induction depends not only on the conformation of the transmitting chain of atoms,

[*] The more important results have been reported in communications [10]; for the preparation of some of the model compounds cf. [11].

[**] By definition [11] the solvent is involved as a nucleophile in a k_s process, not however, in a k_c process [16].

[***] As recently noted [14], k_c processes are anticipated for bicyclic and tricyclic compounds, in which the nucleofuge is adjacent to one of two bridgehead atoms.

[****] The superscript in the symbol σ_I^q indicates that *q*uinuclidines serve as the model.

[*] It was recently reported that the rates of 2-*exo*-norbornyl sulfonates are also more strongly affected by substituents at C1 [8] and at C5 [9] than the rates of the 2-*endo* epimers.

because the bromoadamantanes **17**, which have the same W-like arrangement as the norbornyl tosylates **12**, correlate with a reaction constant ρ of only -1.14. As will be shown in Section 6, the polarizability of the carbon chain also plays an important role.

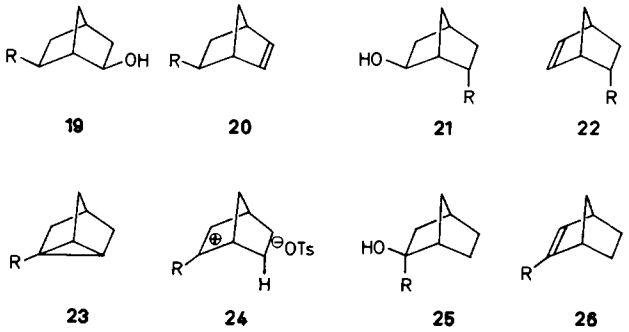
The different sensitivity of rates to substituents at C6 in the series **12** and **13** causes the rate ratios k_{12}/k_{13} to decrease from 2388 for R = *t*-butyl to 0.37 for R = Br (Table 1). But since 6-*exo*-substituents do not substantially change the steric environment of the 2-*endo*-OTs groups in **13**, steric hindrance to ionization, as postulated by *Brown*[1], cannot be the cause of the high k_{12}/k_{13} rate ratio of 425 (Table 1) for the unsubstituted tosylates **12** and **13** (R = H).

Table 1. Rate constants for the solvolysis of some 6-*exo*-substituted 2-*exo*- and 2-*endo*-norbornyl *p*-toluenesulfonates **12** and **13**, respectively, in 80 vol.-% ethanol at 70.0 °C and k_{12}/k_{13} rate ratios [10b].

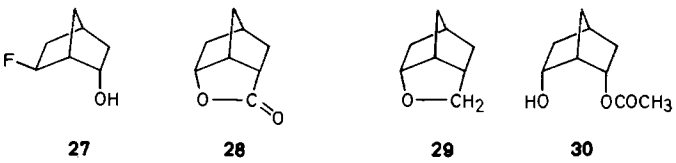
R	k_{12} [s^{-1}]	k_{13} [s^{-1}]	k_{12}/k_{13}
$(CH_3)_3C$	6.09×10^{-2}	2.55×10^{-5}	2388
$COO^{\ominus}$	7.04×10^{-2}	1.16×10^{-4}	607
$(CH_3)_2CH$	2.46×10^{-2}	5.30×10^{-5}	464
H	3.58×10^{-2}	8.42×10^{-5}	425
CH_2NH_2	8.84×10^{-3}	3.75×10^{-5}	236
CH_3	1.09×10^{-2}	6.02×10^{-5}	181
CH_2OH	5.97×10^{-3}	4.39×10^{-5}	136
CH_2Br	1.06×10^{-4}	6.75×10^{-6}	16
$CONH_2$	7.56×10^{-5}	7.12×10^{-6}	11
OH	6.05×10^{-4}	1.00×10^{-4}	6.0
$COOCH_3$	6.33×10^{-6}	1.73×10^{-6}	3.7
CN	1.23×10^{-7}	1.40×10^{-7}	0.88
$OCOCH_3$	8.14×10^{-7}	1.21×10^{-6}	0.67
F	7.21×10^{-7}	1.53×10^{-6}	0.47
Br	1.51×10^{-7}	4.06×10^{-7}	0.37

This conclusion is supported by comparison of the tosylates **12** and **13** (R = H) with their 6-*endo*-alkyl derivatives **14** and **15** ($R = CH_3$ or *t*-butyl). Thus, the methyl group in **14** ($R = CH_3$) reduces the rate by a factor of 6.4 due, probably, to steric hindrance to solvation. The 6-*endo* methyl group in **15** reduces the rate by almost the same factor, namely 7, although ionization should be more strongly hindered according to *Brown*'s hypothesis[1]. Introduction of the even bulkier 6-*endo*-*tert*-butyl substituent in **14** and **15** has a similar effect, *i.e.* a rate reduction of 1.1 and 4, respectively, compared to that of the unsubstituted tosylate. High $k_{2\text{-}exo}/k_{2\text{-}endo}$ ratios must, therefore, have another cause and will be discussed, following an account of the hydrolysis products of the tosylates **12** and **13** in 70% aqueous dioxane.

As a rule, epimeric tosylates **12** and **13** yield different amounts of the same products[20], as is frequently observed in solvolysis reactions involving stereoisomeric ion pairs as intermediates[*]. The products include unrearranged *exo*-alcohols **19** *and* olefins **20**, *and* smaller amounts of their rearranged isomers **21** *and* **22**, *and* the nortricyclene derivatives **23.** As is well known, solvolysis of the unsubstituted 2-*exo*-tosylate **12** (R = H) leads to extensive C6→C2 and C3→C2 hydride shifts, which are only detectable by isotopic labeling[17]. The 6-alkyl derivatives **12** ($R = CH_3$, *i*-C_3H_7, and *t*-C_4H_9) undergo C6→C2 hydride shifts leading to the more stable tertiary carbenium ions **24**, as evidenced by the formation of 50 to 80% of the tertiary alcohols **25** and the olefins **26.**



As mentioned in Section 2, it has hitherto been assumed that 2-norbornyl cations, whether "classical" **6** or "nonclassical" **4**, react almost exclusively on their *exo*-side with nucleophiles[1]. It was therefore surprising to find that several tosylates **12** and **13** led to large amounts of 2-*endo*-substitution products. Thus, the 6-*exo*-fluoride **12** (R = F) yielded 57% of the 2-*endo*-alcohol **27** and only 9% of the 2-*exo*-alcohol **19** (R = F), besides olefins. Furthermore, considerable amounts of *endo*-cyclized products, *i.e.* the lactone **28**, the ether **29**, and the *endo*-diol monoacetate **30** were obtained from both tosylates **12** and **13**, which contained the nucleophilic substituents $COO^{\ominus}$, COOH, $COOCH_3$, $CONH_2$, CH_2OH, and CH_3COO at C6[20]. The hypotheses outlined in Section 2 do not convincingly explain these results, especially in view of the fact that these tosylates have k_{12}/k_{13} ratios between 607 (for $COO^{\ominus}$) and 0.47 (for R = F) (Table 1).



The behavior of the tosylates **12** and **13**, in which R represents an electrofugal group, *i.e.* CH_2NH_2, CH_2OH, $CONH_2$, and $COO^{\ominus}$ is also noteworthy. During heterolytic fragmentation of the type

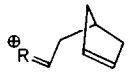
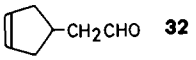
$$a—b—c—d—X \rightarrow a—b + c=d + X:$$

such groups are eliminated as electrofugal fragments $CH_2=\overset{\oplus}{N}H_2$, $CH_2=O$, $HN=C=O$, and CO_2, respectively[22]; hence they act as σ-electron donors. When present in 2-*exo*-tosylates **12**, these substituents cause a fourfold (CH_2NH_2) to hundredfold ($COO^{\ominus}$) increase in rate based on the inductive regression line in Figure 2[*]. Again, these accelerations are more pronounced in the *exo*-compounds **12** than in the *endo*-compounds **13**[10b]. The reason for the exalted polar effects of electrofugal substituents, which are also observed in the 3-bromoadamantane derivatives **17**[18b], is not yet clear. However, they appear to be connected with the increased polarizability of molecules un-

[*] Cf. [21] and references cited therein.

[*] These points have been omitted in Figure 2 for the sake of clarity.

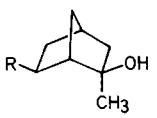
dergoing reaction in a k_c process. It is also striking that substantial amounts of nortricyclene **23** (R = H) and of the corresponding acid **23** (R = COOH) are obtained from the sodium salts **12** and **13** (R = COONa) by 1,3-elimination of CO_2 (homofragmentation) and of a proton at C6, respectively, in addition to the expected hydroxy acids **19** and **25** (R = COOH).

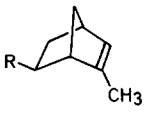
31   **32**

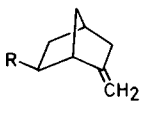
Large accelerations by factors of 40 to 100 are also observed in the reactions of 2-*exo*-tosylates **12** in which R represents an n-electron donor such as CH_3S, CH_3O, HO, or $(CH_3)_2N$[20]. These compounds, however, undergo concerted and therefore accelerated fragmentation[22] to the salts **31**, which are immediately hydrolyzed to (3-cyclopentenyl)acetaldehyde **32**.

5. Tertiary 2-Norbornyl Derivatives

As mentioned in Section 2, it has hitherto been accepted that tertiary 2-norbornyl derivatives **9** and **10** (R = H) react *via* "classical" carbenium ions **11**[*], which do not require intramolecular bridging because of their enhanced stability. Likewise, it seems to be agreed that high k_9/k_{10} rate ratios, also observed in the tertiary series (Table 2), are due to hindered ionization of the *endo*-epimer **10**[1]. However, studies of 6-substituted 2,4-dinitrophenyl ethers **9** and **10**

 **33**

 **34**

 **35**

(X = 2,4-$(NO_2)_2C_6H_3O$) provide reasons to doubt these assumptions [10c]. Thus, not only are *exo*-alcohols **33** obtained exclusively, besides the olefins **34** and **35**, upon hydrolysis

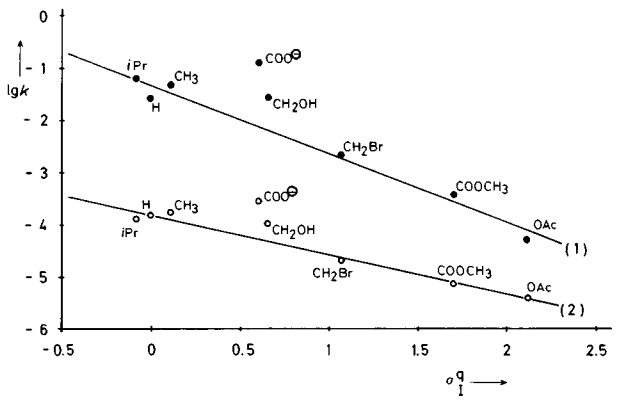


Fig. 3. Plots of lg *k* for the solvolysis of 2-*exo*- (curve 1) and 2-*endo*-2,4-dinitrophenyl ethers (curve 2) of 6-*exo*-substituted 2-methylnorbornanols, **9** and **10**, respectively, against σ_I (80% ethanol, 100°). Points for $COO^{\ominus}$ and CH_2OH are not included in the regression.

[*] The tertiary 2-methyl-2-norbornyl cation **11** (R = H) is an exception, in that *Paasivirta* [30] proposed a "semiclassical" structure analogous to **40** in order to explain the exclusive *exo*-addition of formic acid.

of **9** and **10**, indicating exclusive *exo*-attack of solvent on the intermediate tertiary cations **11**, but it is also significant that lg*k* for the *exo*- and *endo*-ethers, **9** and **10**, respectively, again correlate linearly with the corresponding inductive substituent constants σ_I (Fig. 3). Hence, ionization is also controlled by the I effect of R, and again more strongly in the *exo*-series **9** than in the *endo*-series **10**. This is reflected in the ρ values of -1.30 and -0.75, respectively, which are, as expected, lower than those for the secondary tosylates **12** and **13**.

The different degrees to which rates are controlled by 6-*exo*-substituents in the series **9** and **10** again lead to varying k_9/k_{10} ratios. These approach unity as the $-$I effect of R increases (Table 2). Thus, once again steric hindrance to ionization of the *endo*-2,4-dinitrophenyl ethers **10** cannot be the reason for high k_9/k_{10} ratios. Furthermore in these

Table 2. Rate ratios for 2-*exo*- and 2-*endo*-dinitrophenyl ethers **9** and **10** (X = 2,4-$(NO_2)_2C_6H_3$) in 80 vol.-% ethanol at 100 °C [10c].

R	k_9/k_{10}
$(CH_3)_2CH$	491
$COO^{\ominus}$	439
CH_3	272
CH_2OH	257
H	171
CH_2Br	105
$COOCH_3$	52
CH_3COO	14

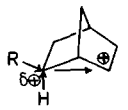
series the electrofugal groups $COO^{\ominus}$ and CH_2OH also exert exalted polar effects, as shown by the deviations of the respective points from the inductive regression line in Figure 3.

6. Inductive Effects and 1,3-Bridging

An interpretation of *exo*/*endo* rate ratios is essential for an understanding of the nature of norbornyl cations. As shown above, these ratios are controlled by the I effect of substituents at C6, and this effect is transmitted more strongly in the secondary series and in the *exo*-tosylates than in the tertiary series and in the *endo*-tosylates. It is particularly important that a linear correlation is observed not only between the lg*k* values for the secondary *exo*- and *endo*-tosylates **12** and **13** and for the tertiary *exo*- and *endo*-ethers **9** and **10**, respectively, but also between the lg*k* values for the secondary and tertiary series[10c]. This fact indicates that the transition states for these reactions differ quantitatively rather than qualitatively. In view of *Winstein*'s hypothesis, as presented in Section 2, the question must therefore be raised whether induction and bridging, hitherto regarded as unrelated, are in fact interrelated phenomena.

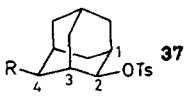
As is well known, conventional valence bond symbols, such as in **12** and **13**, are inaccurate and frequently misleading representations of the actual electron distribution in a molecule. Thus, in norbornane the electrons which form the C6—C1—C2 bonds are not confined to the regions between consecutive atoms; they also occupy much of the space between alternate atoms, *i.e.* C6 and C2. This is made clear by space-filling models which take account

of covalent radii. Provided that the substituents are electron donors, the electrons around C6 will tend to move towards a cationic center at C2, as illustrated by the arrows in **36**. A bonding interaction between C6 and C2, *i.e.* 1,3-bridging, as shown in **40** (Scheme 1) will result, the


36

strength of which should vary according to the relative electronegativities of R and of the cationic C2. 1,3-Bridging should be stronger in a free carbocation than in a contact ion pair, such as **40**, because the anion stabilizes the cation. Strong bridging should also occur in free carbocations generated in non-nucleophilic solvents, as shown by the work of *Olah*[2b]. But it should also occur in k_c processes, where a neighboring carbon atom assumes the function of a nucleophilic solvent and thereby becomes pentacoordinate, while the cationic center becomes tetracoordinate, as in **40**.

A strong indication that donor induction and bridging are related is the increase in *endo*-substitution which is observed in the solvolysis of **12** in the sequence CH_2OH (0%), $COOCH_3$ (28%), CH_3COO (41%), F (57%), *i.e.* with the −I effect of R[19][*]. Electron-attracting (−I) substituents thus hinder bridging and thereby facilitate *endo*-attack at the ion pair **38** (Scheme 1).


37

A further indication for the connection between induction and bridging is provided by a comparison between the tosylates **12** and 4-substituted 2-adamantyl tosylates **37**, which possess the same W-like conformation of the R—C—C—C—OTs chain and which likewise react in a k_c process[23]. In contrast, however, to the norbornyl tosylates **12**, which are already strained, the adamantyl tosylates **37** are unstrained until bridging between C2 and C4 deforms the derived cations. This appears to be one of the reasons why **37** (R = H) reacts almost 7000 times more slowly than **12** (R = H) (Table 4), and why, unlike the latter, it shows little tendency to rearrange[24]. More important is the fact that the reaction constant ρ for the solvolysis of the tosylates **37** in 80% ethanol is only −0.82, *i.e.* much smaller than for the tosylates **12** (−2.0). Hence, the less bridging and rearrangement, the less the rate depends on the inductive effect of the substituent. Induction and bridging do indeed appear to be related.

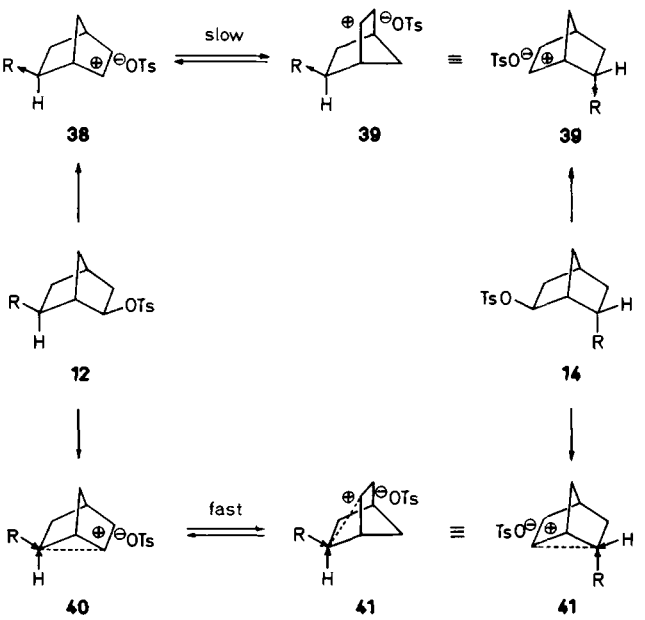
7. Epimeric or Enantiomeric Norbornyl Cations

The reaction rates of 6-*endo*-substituted 2-*exo*-tosylates **14** are almost as dependent upon the I effect of R as the rates of their epimers **12**. This follows from the somewhat smaller ρ value of −1.76 and the k_{12}/k_{14} ratios which are close to one (Table 3). The directional effect of the substituent at C6 is therefore small. However, hydrolysis of C6-epimeric tosylates **12** and **14**, where R = H or alkyl, leads

Table 3. Rate ratios for 6-*exo*- and 6-*endo*-substituted 2-*exo*-norbornyl *p*-toluenesulfonates **12** and **14**, respectively, in 80 vol.-% ethanol at 70 °C [20b].

R	k_{12}/k_{14}
H	1
CH_3	1.95
$(CH_3)_2CH$	5.7
$(CH_3)_3C$	1.8
CH_2Br	0.39
F	1.54
Br	0.77
CN	2.84

to *identical* mixtures of products, whereas *different* mixtures of products are obtained when R = CH_2Br, F, Br, and CN[20b]. This proves that the products have a common origin in the first case, but are formed from different intermediates in the second. The latter must be the C6-epimeric ion pairs **38** and **39**[*] which react faster with water than they equilibrate (Scheme 1). Therefore, −I substituents not only hinder bridging, they also reduce the rate of the Wagner-Meerwein rearrangement. It is, therefore, appropriate to call these norbornyl cations "classical".



Scheme 1.

It is conceivable that the epimeric 6-alkyl 2-*exo*-tosylates **12** and **14**, which yield identical product mixtures, ionize directly to the doubly bridged "nonclassical" cations **42a** and **42b**, for these are enantiomers. On the other hand, it seems improbable that an overall asymmetric cation, such as the 6-*tert*-butyl derivative, would be symmetrically bridged, as in **42** (R = *t*Bu). This is more likely to be the

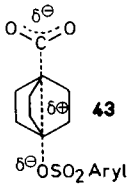
[*] In a strict sense *endo* attack of water at C2 should not be compared to *endo*-cyclization by nucleophilic substituents at C6, because the latter is a favored intramolecular process.

[*] Only one possible enantiomer is shown.

case when R = H. But the fact that the k_{12}/k_{13} ratio is 425 when R = H and 2388 when R = *t*Bu (Table 1) militates against this possibility; because if symmetry were to confer special stability to carbocations, the k_{12}/k_{13} ratio should be larger for R = H. But there are further reasons to reject symmetrical bridging even for the unsubstituted norbornyl cation, such as the fact that **12** (R = H) correlates equally well with σ_1^+ as do its 6-substituted derivatives (Fig. 2) and the fact that nortricyclene **23** (R = H) is approximately twice as strained as norbornane[25]. A considerable part of this strain would be conserved in the cation **42**, even though the partial bonds are longer than in **23**. The results for the tosylates **12**, **13**, **14** and **15**, therefore, do not make it necessary to postulate a different kind of bonding for the unsubstituted norbornyl cation.

The alternative to symmetrical bridging is asymmetrical or 1,3-bridging, as exemplified by the cations **40** and **41** which, by graded bonding between C6 and C2, merge with the unbridged cations **38** and **39**[10e]. The formulations **40** or **36** are preferred to *Winstein*'s "nonclassical" formula **42**[3] because they convey that the C2—C6 bond is longer and therefore weaker than the C1—C6 bond and that donor substituents at C6 enhance 1,3-bridging and hence ionization rates. A large part of the positive charge generated in the transition state is transferred to these substituents, as evidenced by the enormous increase in reaction rate by a factor of 10^5 to 10^6 when a halogen atom at C6 in **12** is replaced by *tert*-butyl (Table 1). The positive charge is also delocalized to other adjacent atoms. However, as shown by *Brown et al.*[26], less charge is transferred to C1 than is implied by formula **42**.

C atom participation should not be restricted to 1,3-bridging, as in **40**, as long as it can take place at the rear of an incipient cationic center in a k_c process. This is exemplified by the abnormally large rate increase which results when hydrogen at C4 of the bicyclo[2.2.2]octyl sulfonate **18** is substituted by COONa and which can be attributed to weak 1,4-bridging, as expressed in **43**[18d][*].



1,3-Bridging is very strongly in evidence in the solvolysis of the sodium salt of the 2-*exo*-tosyloxycarboxylic acid **12** (R = COONa), which reacts 100 times faster than the rate calculated on the basis of the σ_1^+ value for $COO^{\ominus}$[20a]. The k_{12}/k_{13} ratio of 607 (Table 1) indicates that ionization is strongly assisted by electron donation from the electrofugal $COO^{\ominus}$ group. As foreshadowed by the bridged structure of the intermediate **40** (R = COONa), more than 20% of the nortricyclenes **23** (R = H and COOH) are formed by elimination of CO_2 and a proton, respectively.

When the solvolysis of 2-*exo*-norbornyl tosylate **12** (R = H) is carried out in the presence of KOH the yield of nortricyclene **23** (R = H) is 40%, while the 6-*endo*-cyano derivative **14** (R = CN) yields 80% of **23** (R = CN) even in the absence of base. However, the orientation of the C6—H bond has little effect on the ionization rate, as the nearly equal rates of 6-*exo*- and 6-*endo*-substituted norbornyl tosylates **12** and **14**, respectively, show.

1,3-Bridging can reduce the energy barrier to interconversion of the cations **40** ⇄ **41** (Fig. 1) to the point where their equilibration becomes faster than their capture by solvent. An energy barrier of *ca.* 2.5 kcal/mol corresponds to a skeletal vibration of frequency 1000 cm^{-1}[*] in which case the cations should behave like enantiomers.

8. *exo*/*endo* Rate Ratios and 1,3-Bridging in Bicyclic Compounds

The results described so far indicate that induction by donor substituents at C6 leads to 1,3-bridging. They do not, however, explain why the k_{12}/k_{13} ratio for the unsubstituted tosylates **12** and **13** (R = H) is so high, namely 425 (Table 1), for both epimers contain a methylene group in the β-position to the incipient cationic center. A steric effect was ruled out in Section 4. The question therefore arises whether a stereoelectronic effect is responsible for the different reactivity of these epimers.

Winstein assumed that in the antiperiplanar arrangement of the *exo*-brosylate **1** the electrons forming the C1—C6 bond are far more effective in assisting ionization than in the *gauche* arrangement which is present in the *endo*-brosylate **2**[3]. Apparently, he did not envisage the participation of the C1—C7 bonding electrons in the ionization of **2**, presumably because they deviate from the plane comprising C1, C2, and OBs by *ca.* 30°. It was therefore essential to test whether this deviation, *i.e.* a stereoelectronic factor, provides a satisfactory explanation for the k_{12}/k_{13} ratio of 425. This could only be accomplished by studying other bicyclic tosylates.

Molecular models of the epimeric bicyclo[3.2.1]oct-8-yl tosylates **44** (Table 4) show that neither the *exo*-C—OTs nor the *endo*-C—OTs bond[**] deviates significantly from the planes comprising the C1—C2 and C4—C5 bonds in the *exo*-tosylate, the C1—C7 and C5—C6 bonds in the *endo*-tosylate. Despite their stereoelectronic equivalence the epimeric tosylates **44** react at widely different rates, the k_{exo}/k_{endo} ratio being 1125 at 130 °C[10f][***], *i.e.* 562 per antiperiplanar CC-bond. Since the k_{exo}/k_{endo} ratio for the epimeric 2-norbornyl tosylates **45** is 425 at 70 °C (and 550 at 40 °C) the conclusion must be that a stereoelectronic

[*] A less satisfying explanation is offered in [18d].

[*] From his study of the deuterium isotope effect on the ^{13}C-NMR spectrum of the norbornyl cation under stable ion conditions, *Saunders* has concluded that the energy barrier is less than 3 kcal/mol and that a static, symmetrical structure is consistent with this result [27].

[**] In formulas **44**—**47** (Table 4), *exo* and *endo* denote the corresponding OTs and OH groups.

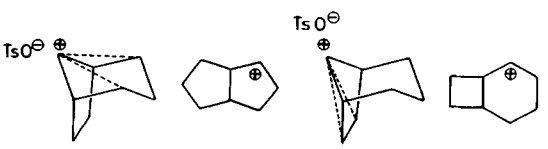
[***] According to *Foote* and *Woodward* [28] k_{exo}/k_{endo} for acetolysis of the tosylates **44** is 1500 at 100 °C.

Table 4. Strain energies of some bicyclic *p*-toluenesulfonates and the k_{rel} values, k_{exo}/k_{endo}, rate ratios of their solvolysis in 80 vol.-% ethanol at 40 °C (**44** at 130 °C).

Compound		k_{rel}	$\frac{k_{exo}}{k_{endo}}$	Strain energy [13] [kcal/mol]	
	44	*exo* 5.1 *endo* $4 \cdot 10^{-3}$	1275	12.1	
	45	*exo* 6790 *endo* 12.4	548	17	
	46	*exo* 400 *endo* 31	13	12.1	
	47	*exo* 523 *endo* 361	1.45	15	
	48	1046	1	13	
	49	1		7	

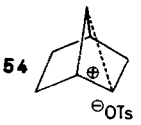
factor alone does not account for a high *exo/endo* rate ratio.

The additional factor, however, could be differential angle strain attending 1,3-bridging in the ionization of an epimeric pair of tosylates, such as *exo*- and *endo*-**44** or **45**[10f]. Thus, the bridged cation **52** from the *endo*-tosylate **44** is much more strained than the bridged cation **50** from the *exo*-tosylate **44.** The former will therefore be only weakly bridged. Rearrangement of these cations should yield the cations **51** and **53,** respectively, the latter being again more strained due to the cyclobutane ring. The *exo*-tosylate **44** actually leads to 86% of alcohols and olefins derived from the bicyclo[3.3.0]oct-2-yl cation **51,** beside 14% of *exo*-alcohol **44** from the unrearranged cation **50.** On the other hand, the *endo*-tosylate **44** does not yield products derived from the rearranged and far more strained bicyclo[4.2.0]oct-2-yl cation **53.** In fact, they are also derived from **50** (38%) and **51** (62%). The fact that the more reactive *exo*-tosylate **44** cannot form a symmetrically bridged "nonclassical" ion of the *Wilson-Winstein* type **42** deserves special attention.



50 **51** **52** **53**

Large differential bridging strains are apparent in the ionization of 2-*exo*- and 2-*endo*-norbornyl tosylate **45.** Thus, bridging of C6 in the *exo*-ion pair **40** (R = H, Scheme 1) causes only slight additional strain, which remains constant in the subsequent degenerate rearrangement to **41.** On the other hand, bridging of C7 in the *endo*-ion pair **54,** and especially its rearrangement to the bicyclo[3.1.1]oct-2-yl cation **55,** would entail a considerable increase of angle strain due to formation of the cyclobutane ring. It is therefore not surprising that none of the products (mostly 2-*exo*-norbornanol[20a]) derive from **55**[10f].



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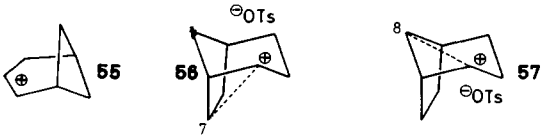
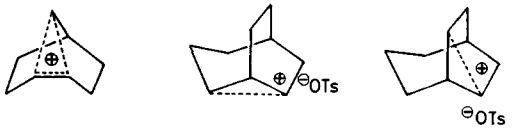
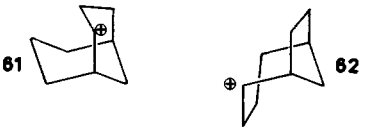
In this view the rates of epimeric and stereoelectronically equivalent compounds should be similar in cases where bridging strains are comparable. This is exemplified by the 2-*exo*- and 2-*endo*-bicyclo[3.2.1]octyl tosylates **46,** the *exo/endo* rate ratio of which is only 13 (Table 4). Bridging of C7 in the *exo*-tosylate leads to the cation **56,** in which the seven-membered ring is contracted to a *quasi* six-membered ring. On the other hand, bridging of C8 in the *endo*-tosylate leads to the cation **57,** in which the six-membered ring is contracted to a slightly more strained five-membered ring. The latter example is of special significance because symmetrical bridging would lead to the totally symmetric cation **58.** Being "nonclassical" in the *Wilson-Winstein* sense, it should be exceptionally stable and therefore be formed more rapidly. In fact the *endo*-tosylate **46** reacts 13 times more slowly than the *exo*-epimer, which cannot form **58** directly. Hydrolysis of the *exo*-tosylate **46** to the *exo*-alcohol **46** occurs with retention and is accompanied by rearrangement to bicyclo[2.2.2]oct-2-yl tosylate **48** and the formation of the corresponding alcohol **48.** The *endo*-tosylate **46,** however, yields 92% of the *endo*-alcohol with retention, besides 8% of the *exo*-alcohol with inversion[10f][*].



55 **56** **57**



58 **59** **60**



61 **62**

The epimeric 6-*exo*- and 6-*endo*-bicyclo[3.2.2]nonyl tosylates **47** (Table 4) are again stereoelectronically equivalent. Moreover, models do not indicate different bridging strains in the cations **59** and **60.** It is therefore not surprising that the *exo/endo* rate ratio is only 1.45. Again, it is the larger *exo*-bridge which provides stronger assistance to ionization. The products of both tosylates **47,** *i.e.* alcohols

[*] The acetolysis of the epimeric tosylates **46** was previously studied in detail by *Goering et al.* [29].

and olefins, derive from the rearranged cations **61** and **62**. Finally, the stereoisomers of bicyclo[2.2.2]oct-2-yl tosylate **48** are enantiomers and therefore chemically equivalent.

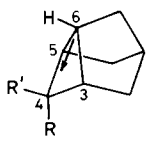
Table 4 also lists some relative reaction rates (k_{rel}) and calculated strain energies[13]. The former are based on 2-adamantyl tosylate **49**, because it shows the least tendency to bridge and to rearrange. The absence of a relationship between *exo/endo* rate ratios and strain energies is striking and particularly noticeable when comparing the tosylates **44** and **45**. On the other hand, the most strained tosylates, namely *exo*-**45**, *exo*-**47** and **48**, which should therefore be most inclined to bridge, react the fastest. But the strikingly low rates of the tosylates **44** clearly indicate that further factors contribute to the reactivity of bicyclic compounds, such as hyperconjugation of β-CH bonds which, for stereoelectronic reasons, is hindered in the bicyclo[3.2.1]oct-8-yl cations **50** and **52**, and by steric resistance towards an increase of the bond angle C1C8C5.

9. Conclusions and Outlook

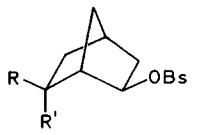
After many years of discussion whether solvolytically generated 2-norbornyl cations are unbridged or bridged, *i.e.* classical or nonclassical, it is now evident that the question is faulty, in that these terms denote only the structural extremes of a graded series. Thus, the high k_{12}/k_{13} rate ratio of 425 and the formation of racemic 2-*exo*-norbornanol from optically active 2-*exo*-norbornyl tosylate **12** (R = H) point to a strongly bridged intermediate. However, the latter is not necessarily a static, symmetrically bridged cation, such as **42** (R = H), for high *exo/endo* rate ratios and retention of configuration are also observed when symmetrical bridging must be excluded for structural reasons (see the *exo*-tosylate **44**). Therefore, very rapidly equilibrating 1,3-bridged cations **40** ⇄ **41** are preferred to **42** (R = H). On the other hand, electron-attracting substituents at C6 reduce bridging and the rate of rearrangement to the point where the *exo/endo* rate ratio falls below one (Table 1) and 2-*endo*-substitution products are also formed.

Intramolecular 1,3-bridging, as postulated here, is due to the absence of nucleophilic solvation during the formation of bicyclic cations. It is especially pronounced in the strained and hence easily polarized 2-norbornyl cation. When 1,3-bridging in the transition state of epimers differs widely due to differential bridging strain, as for **12** and **13** (R = H), the rates will also differ considerably, and this leads to high *exo/endo* rate ratios.

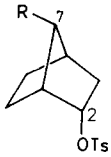
An extremely large difference in rate of more than 500000 was observed for the epimers **63a** and **63b** of tricyclo[3.2.1.$0^{3,6}$]oct-4-yl methanesulfonate[31]. The higher reactivity of **63a** was ascribed to stronger bridging between C4 and C6 in the transition state for this epimer; for only here is C6 approximately coaxial with respect to the C4—OSO_2CH_3 bond. Furthermore, the C4—C6 distance is reduced due to puckering of the cyclobutane ring, which leads to stronger 1,3-bonding in the incipient cation[*]. *Bauld* has provided a quantum mechanical explanation for the stabilization of cyclobutyl and 2-norbornyl cations[32], which closely resembles the concept of 1,3-bridging as developed here.



63a, R = CH_3SO_2O, R' = H
63b, R = H, R' = CH_3SO_2O



64a, R = D, R' = H
64b, R = H, R' = D



65

It should also be mentioned that the unusually large kinetic isotope effects (for γ-deuterium) observed in the solvolysis of 6-deuterated 2-*exo*-norbornyl brosylates **64a** and **64b**[33] likewise point to a strong interaction between C2 and C6 in the transition state.

The fact that differential bridging strain explains, at least qualitatively, the different reactivity of the epimeric sulfonates mentioned above should stimulate the study of other pairs of epimers. Thus, it is to be expected that 1,3-bridging will be unfavorable for 7-*anti*-substituted 2-*endo*-norbornyl tosylates **65** because it entails the formation of a *quasi* four-membered ring. A considerably less negative reaction constant is therefore anticipated as compared to the more easily bridged tosylates **12** ($\rho = -2.0$).

In view of the postulated connection between inductive charge transfer and bridging (Section 6) it would also seem desirable to investigate the effects of substituents in other bicyclic systems. The object is to determine their influence on reactivity (expressed as ρ values) as a function of the charge at the reaction center, the distance and orientation of the bridging atom, and the conformation of the intervening chain. Such studies should eventually lead to a better understanding of the mechanism of transmission of polar effects in saturated molecules.

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[*] The cation from **63a** and **63b** subsequently undergoes a cyclobutylcyclopropylcarbonyl-homoallylic rearrangement; see [31].

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Lewis Acid Induced α-Alkylation of Carbonyl Compounds

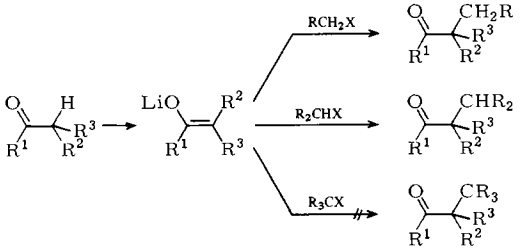
New synthetic methods (35)

By Manfred T. Reetz*

Carbonyl compounds undergo α-alkylation *via* the corresponding silyl enol ethers using S_N1 active alkyl halides or acetates in the presence of Lewis acids. This methodology extends the scope of carbonyl chemistry considerably, since S_N1 active alkylating agents are generally base sensitive and therefore unsuitable for reactions with enolate anions or nitrogen analogs. A prime example is the α-*tert*-alkylation of aldehydes, ketones and esters.

1. Introduction

The α-alkylation of carbonyl compounds is an important C—C bond forming reaction[1]. With the aid of a strong base the carbonyl compound is converted into the enolate anion, which in turn undergoes S_N2 reactions with proper alkyl halides or tosylates (Scheme 1). The same applies to nitrogen analogs such as deprotonated Schiff bases, oximes or hydrazones. Unfortunately, the pronounced basicity of these nucleophiles imposes limits on the variation of the alkylating agents. Only S_N2 active compounds such as methyl, allyl, benzyl, and some primary alkyl halides consistently afford good to excellent yields[1]. In these cases such problems as polyalkylation[2], lack of regiospecificity in the case of unsymmetrical ketones[1,2] or low stereoselectivity[3] have been solved to some extent. In contrast, many secondary alkyl halides undergo competing base-induced HX-elimination, the extent of which depends upon the pK_a value of the ketone[4]. The amount of undesired olefin formation can vary up to 100% even in the case of isopropyl iodide. Furthermore, secondary alkyl halides react slowly, so that regiospecificity is not always ensured[1]. The detour *via* metalated hydrazones is often recommended, but has the disadvantage that in case of unsymmetrical ketones only the less substituted α-position can be alkylated[1]. Tertiary alkyl halides are completely unsuitable because the basic enolate anions cause rapid HX-elimination[1]. Even the less basic enamines fail to undergo C—C bond formation[5]. Thus, until recent times α-



Scheme 1.

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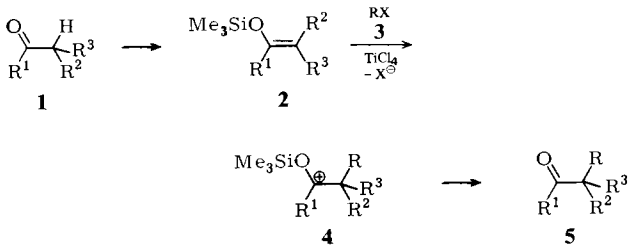
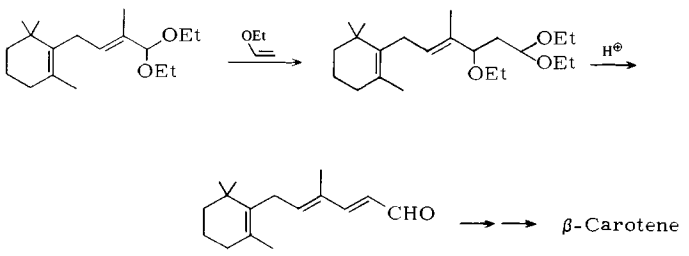
tert-alkylated carbonyl compounds were accessible only indirectly *via* several steps[6].

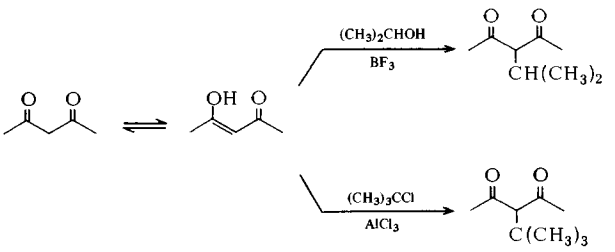
We recently found a simple solution to the above problems and have been able to considerably extend the area of carbonyl chemistry. The carbonyl component **1** is first converted into the electron-rich but non-basic silyl enol ether **2**. A variety of excellent silylation procedures is known[7], including the very mild reaction of carbonyl compounds with ethyl trimethylsilylacetate in the presence of tetra-*n*-butylammonium fluoride[7c] or with trimethylchlorosilane/triethylamine in the presence of sodium iodide[7d] at *room temperature*. The actual C—C bond formation **2**→**5** is accomplished by using suitable alkyl halides **3** in the presence of such Lewis acids as $TiCl_4$, $SnCl_4$ or ZnX_2[8]. Lewis acid promoted ionization of **3** to form the corresponding carbocation R^+ is plausible, which is trapped by the silyl enol ether **2**. The initial addition product **4** is rapidly desilylated, making oligomerization impossible. *This means that not only tertiary alkyl halides, but all* S_N1 *active species should be excellent alkylating agents*[9, 10]. It is important to stress that it is precisely this class of alkylating agents which fails or seldom works in classical enolate chemistry. S_N2 reactions of basic enolates on the one hand, and Lewis acid induced C—C bond formation using silyl enol ethers are thus complementary methodologies.



The predecessor of the above concept is the BF_3 mediated "aldol addition" of acetals to vinyl ethers, discovered in 1939[11a]. This process[11b] was used in the key-step of the Roche synthesis of β-carotene and similar compounds[11c].

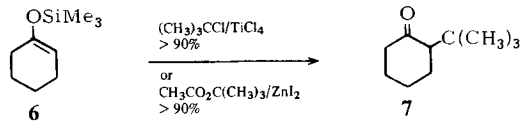


Later, *Mukaiyama* replaced alkyl enol ethers by silyl analogs and carried out an impressive series of aldol additions with acetals, aldehydes and ketones[12]. Mechanistically related are also the isopropylation and *tert*-butylation of certain 1,3-dicarbonyl compounds (14—68% yields) under Friedel-Crafts conditions as reported by *Hauser et al.*[13a] and *Boldt et al.*[13b]. Finally, the synthetically useful "Friedel-Crafts" reactions of carbocations with chlorinated olefins according to *Schmerling*[14] and *Bott* and *Hellmann*[15] are worthy of mention.

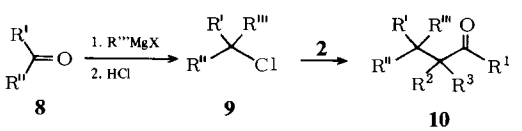


2. α-*tert*-Alkylation of Carbonyl Compounds

As a result of careful optimization, we discovered that the α-*tert*-butylation of the silyl enol ether **6** derived from cyclohexanone occurs rapidly and with high conversion (90%) if $TiCl_4$ is used as the Lewis acid at −30 °C to −60 °C in dichloromethane[8, 16a]. When carrying out the reaction, an equivalent amount of $TiCl_4$ is added rapidly to a mixture of **6** and *tert*-butyl chloride, followed by aqueous work-up after about two hours. If the silyl enol ether is added to a mixture of $TiCl_4$ and *tert*-butyl chloride, conversion is only 50—60%[16a], a variation which was independently described by *Chan et al.*[17]. Other ways of carrying out the reaction are also inferior, *e.g.*, addition of *tert*-butyl chloride to a mixture of **6** and $TiCl_4$[16b]. Besides $TiCl_4$, milder Lewis acids such as $SnCl_4$ (equivalent amounts at 0 °C) or $ZnCl_2$ (catalytic amounts at room temperature) are effective (≈90% and >70% conversion, respectively[6]). *Tert*-butyl acetate and *tert*-butyl methyl ether also behave as alkylating agents in $TiCl_4$-induced reactions, but the yields are lower (30—55%)[6]. In contrast, C—C bond formation is particularly smooth with *tert*-butyl acetate if ZnI_2 is used as the Lewis acid, *e.g.*, **6**→**7** to the extent of >90%[18]. Unfortunately, more complex acetates often show significant amounts of undesired elimination[*].



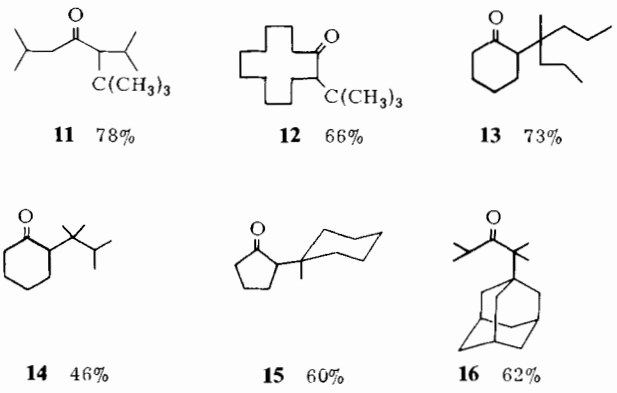
Not only *tert*-butyl chloride, but practically all *tert*-alkyl halides **9** are effective[19], thereby providing a new and simple method for the geminal dialkylation of ketones **8**→**10**. Quaternary carbon atoms not only occur frequently in natural products[20], but also in synthetic fragrances (*e.g.*, **7**)[21], pharmacologically active substances[22], and theoretically[23] and spectroscopically interesting compounds[24]. So far not many α-*tert*-alkylations of aldehydes have been carried out[6, 8, 17].



[*] Examples are methylcyclopentyl and methylcyclohexyl acetate.

2.1. Variation of the *tert*-Alkyl Halide and the Ketone

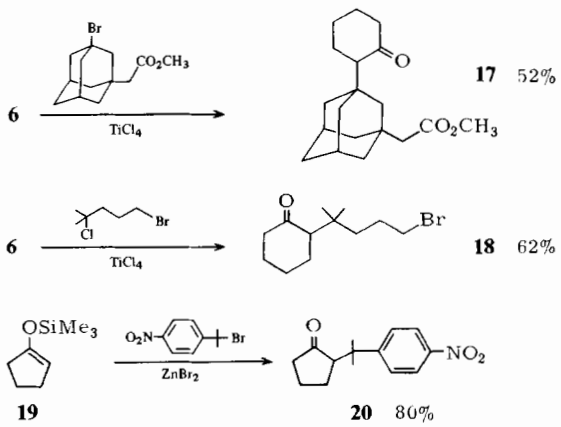
We have successfully alkylated a large number of ketones with structurally different *tert*-alkyl halides[19,25]. (The figures next to the numbers of the compounds refer to yields of isolated products in the alkylation of the corresponding silyl enol ethers.) It is important to note that branched alkyl halides do *not* undergo undesired *Wagner-Meerwein* rearrangements which would lead to a loss of positional specificity (see **13**, **14**, and **15**)[19,25]. Reactive bridgehead alkyl halides also participate (see for example **16**)[19,26], but not such strained compounds as 1-bromobicyclo[2.2.2]octane[27]. Undesired di- or polyalkylation does not occur. However, a second *tert*-alkyl group can be introduced by a stepwise procedure if so desired. In this case, α,α'-, but not α,α-dialkylation is possible[19].

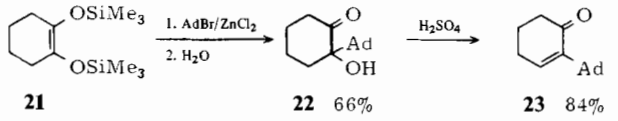


2.2. Chemoselectivity

The process of alkylation is not disrupted if the *tert*-alkyl halide contains such additional functional groups as aryl (*cf.* **19**→**20**)[28], alkoxycarbonyl (cf. **6**→**17**)[19], alkenyl[27], ω-bromoalkyl[19] (cf. **6**→**18**) or nitro groups[28] (cf. **19**→**20**). In some cases $TiCl_4$ should be replaced by milder Lewis acids such as ZnX_2. The reaction of *p*-nitrocumyl chloride leading to **20** is complementary to the reactions described by *Kornblum*, in which soft, resonance stabilized carbanions are required[29]. The latter reactions are radical processes.

Certain additional functional groups in the ketone component likewise pose no problems, *e.g.*, aryl[19], alkenyl[27], and hydroxy groups[27], the latter being protected in the silylated form. For example, α-hydroxy ketones (acyloins) can be α-*tert*-alkylated using the bis-silylated form **(21**→**22)**. Dehydration affording the α,β-unsaturated ketone (here **23**) is possible[27].

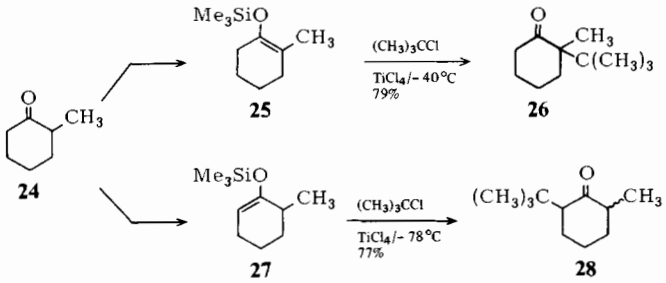




Ad = 1-Adamantyl

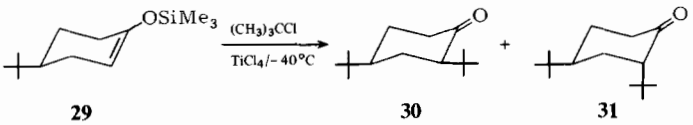
2.3. Regiospecificity in Unsymmetrical Ketones

Since unsymmetrical ketones can be converted selectively into the "kinetic" or "thermodynamic" silyl enol ether[7], the possibility of regiospecific α-*tert*-alkylation arises. The first system to be studied was 2-methylcyclohexanone **24**[8,17,19]. The reactions **25**→**26** and **27**→**28** are 100% and 89% regiospecific, respectively. Acyclic ketones behave similarly[19]. However, if the reactive centers of the components are extremely sterically hindered, complete loss of regiospecificity may ensue[27,30]. The high yield of isolated product **26** is rather astounding, since the compound is a hexasubstituted ethane with two neighboring quaternary carbon atoms. The method was also found to lead to products having this structural characteristic in a number of other cases[8,17,19].

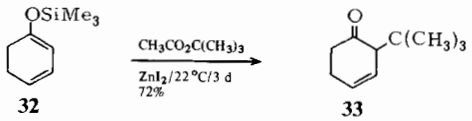


2.4. Diastereo- and Regioselectivity

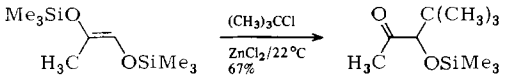
The *tert*-butylation of **29** yielding 85% of **30** and 15% of **31** shows that equatorial attack is preferred[31]. This is in complete contrast to methylation or ethylation of the corresponding lithium enolate, which show no diastereoselectivity (1:1 mixtures)[32]. Although different reaction types (S_N1 and S_N2 reactions) are involved, steric factors are likely to be responsible.



Concerning α,γ-selectivity in α,β-unsaturated ketones, we found exclusive α-alkylation, *e.g.*, **32**→**33**[27].



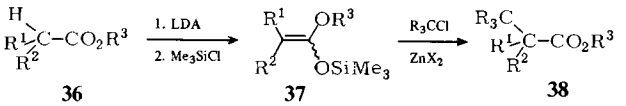
In the case of unsymmetrical bis-silylated acyloins, complete regioselectivity results, since only the "Markovnikov products" are observed[27], *e.g.*, **34**→**35**. Homologous compounds of the type **35** have been used by *Heathcock* in stereoselective aldol additions[33].



34 **35**

2.5. α-*tert*-Alkylation of Carboxylic Acid Esters

Whereas little is known about the α-*tert*-alkylation of aldehydes[6,8,17], that of carboxylic acid esters **36** has been studied in greater detail[26,35]. In these cases the corresponding *O*-silylated ketene ketals **37** are reacted with *tert*-alkyl halides or acetates in the presence of catalytic amounts of ZnX_2 (X = C, Br, I) in dichloromethane or nitromethane. $TiCl_4$ or $SnCl_4$ are unsuitable, since they are reduced by the electron-rich double bond of the silyl enol ether[35].



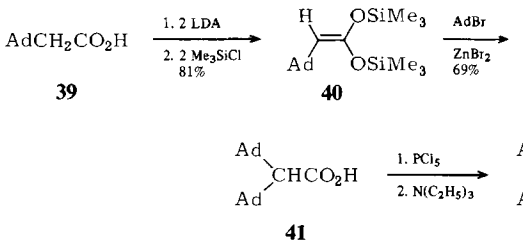
36 **37** **38**

In the case of *tert*-butyl chloride and 1-adamantyl bromide the yields of **38** are good (60—85%)[26,34]; however, with branched alkylating agents they are only 20—60%[35,36]. In nitromethane the reactions are faster and the yields higher than in dichloromethane. If *both* reaction partners are sterically demanding, the reaction may not occur at all[35,36].

In contrast, ZnX_2-mediated α-alkylation of **37** with aryl-activated acetates of the type $ArylR_2COAc$ is unexpectantly smooth[35]. Since the analogous reactions with silyl enol ethers often fail, a radical process may be involved[35]. Generally, the ester component can be varied over a wide range. An exception pertains to the parent compound (ethyl acetate), the silyl ketene ketal of which undergoes rapid ZnX_2-induced rearrangement to the *C*-silyl derivative which is not capable of alkylation[34].

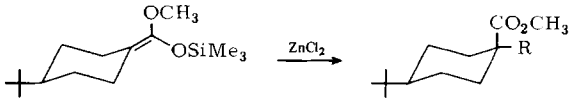
It is also possible to employ carboxylic acids themselves. They are first bis-silylated *via* the corresponding dianions before the actual *tert*-alkylation is performed[35]. The adamantylation of adamantylacetic acid **39**[37] is an example which also shows that compounds having *two* quaternary carbon atoms at *one* center are accessible[35]. This unusual property of the method is restricted mainly to the adamantyl group[26]. The yields in the case of *tert*-butyl chloride is in the order of 20—30%, since HCl-elimination predominates. Noteworthy is the smooth conversion into diadamantylacetic acid **41** and the theoretically interesting diadamantyl ketene **42**[35], both of which are new compounds.

In the α-*tert*-alkylation of **43** the axial ester **44** is the sole product, the stereochemistry of which was proven by X-ray analysis[38]. In contrast, diastereoselectivity in the



39 **40** **41** **42** 80%

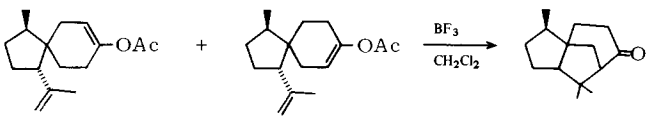
methylation of the corresponding lithium enolate (84 : 16) or the dilithium salt (1 : 1) is lower[39].



43 **44a**, R = 1-Adamantyl
44b, R = $C(CH_3)_3$

2.6. Intramolecular α-*tert*-Alkylation of Carbonyl Compounds

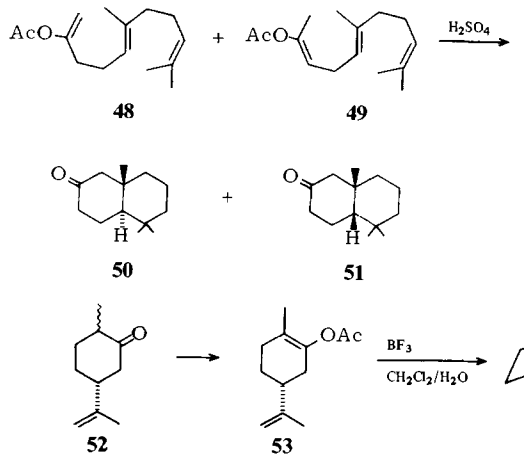
The literature contains only isolated cases of reactions which may be viewed as intramolecular α-*tert*-alkylations. *Corey*'s BF_3-induced cyclization of the acetate mixture **45** and **46** leading to **47** is a prominent example[40a]. Presumably the solvent (methylene chloride) contained water which provided the necessary protons. Addition of methyllithium to **47** completes the synthesis of (±)-cedrol. *Stork* and *Grieco* described several related reactions in which ketones containing olefinic functions undergo BF_3-mediated cyclizations[40b]. They also exploited $SnCl_4$-induced ring opening of cyclopropyl ketones, a process which generates tertiary carbonium ions and tin enolates within one molecule, thereby triggering intramolecular α-*tert*-alkylation[40b].



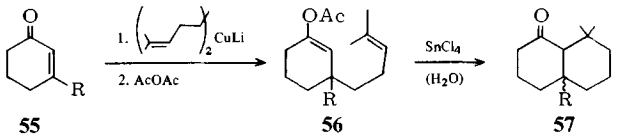
45 **46** **47**

As part of their studies concerning the synthesis of fragrances, *Ohloff et al.* used H_2SO_4 to cyclize the enol acetates **48** and **49** with the formation of decalones **50** and **51**[41]. The total yield was 30% and the diastereomeric ratio 84 : 16. An interesting biomimetic cyclization involving the acetate **53** derived from dihydrocarvone **52** has been reported by *Money et al.*[42]. At high dilution conversion to camphor **54** is ≈90%, but the product was found to be racemic. The isopropenyl group in **53** is probably protonated, generating carbocations which undergo racemizing, reversible 1,2 hydride shifts prior to intramolecular capture by the enol acetate.

Systematic studies of intramolecular α-*tert*-alkylations have only recently been initiated[43]. The starting point was the cyclization of the enol acetate **56a** obtained from cyclohexenone **55a**[43b]. Various Lewis acids such as BF_3, $SnCl_4$ and $TiCl_4$ were tested in moist dichloromethane at room temperature. $SnCl_4$ turned out to be the Lewis acid of choice. Conversion to **57a** was about 60%, from which

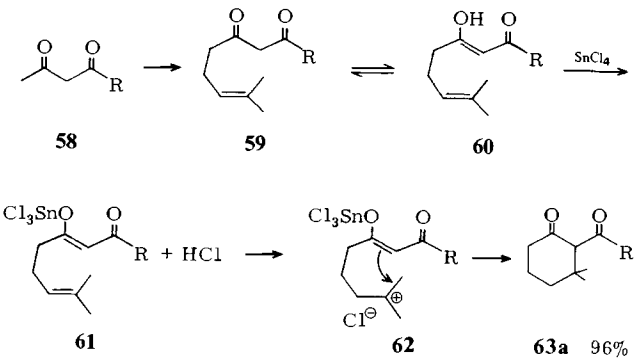


50% was isolated in analytically pure form. If the enol acetate bears an additional methyl group (*e.g.*, **56b**), intramolecular α-*tert*-alkylation to form **57b** is particularly smooth (>90% conversion; 80% isolated). With the assumption of a chair conformation, preliminary studies using NMR shift reagents seem to point to the *cis* form[43b]. However, a definite assignment has not been made.



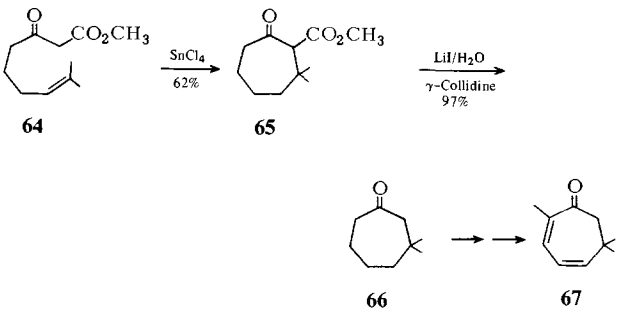
a, R = H; **b**, R = CH_3

A second strategy makes use of simple starting materials such as acetoacetic ester **58a** or acetylacetone **58b**[35,43a,c]. It is known that the dianions of these compounds are readily alkylated at the less resonance stabilized carbon atom[44]. Prenylation affording **59** is thus possible. The ac-

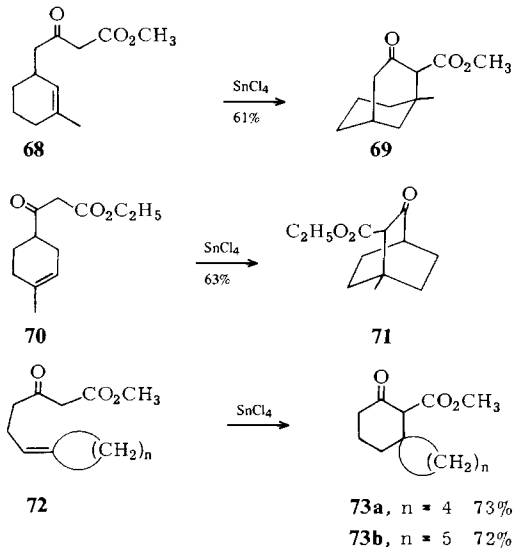


a, R = OCH_3; **b**, R = CH_3

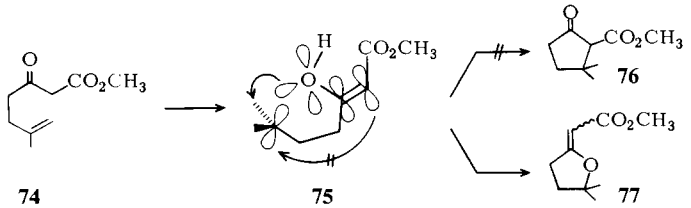
tual intramolecular α-*tert*-alkylation is mediated by catalytic amounts of $SnCl_4$. *O*-Stannylation of the enolized form **60** generating **61** and HCl followed by protonation of the double bond seems reasonable[43a]. Species **62** contains an electron-rich enol function and a tertiary carbocation, so that cyclization to **63** should result. Indeed, this reaction is almost quantitative after about 12 hours. Other catalysts such as $TiCl_4$, HCl or acidic ion-exchange resins are also effective, but result in lower yields[43c]. Although it is not clear whether the Baldwin rules are theoretically well founded in the case of cations, the cyclizations discussed here may formally be regarded as 6-*endo*-trigonal processes[45]. *Weiler* et al. have recently described the cyclization of **59a** independently of us[46]. They made elegant use of **63a** in a synthesis of mokupalide[46]. **63b** is a key compound in the Näf-synthesis of γ-damascone[47] and was synthesized by copper-catalyzed 1,4-Grignard addition to **55b** followed by acylation (30% overall yield)[47]. Thus, the present synthesis utilizing **59b** is an attractive alternative. The $SnCl_4$-mediated cyclization is also useful in other cases, *e.g.*, in the "allowed" 7-*endo*-trigonal reaction of **64** to **65**[43a]. Decarboxylation of **65** affords **66**, which is a precursor of the terpene eucarvone **67**[43a].



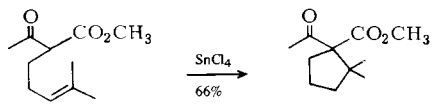
More complex systems undergo analogous intramolecular α-*tert*-alkylations. Thus, bicyclic compounds **69** and **71** as well as spiro derivatives **73** are easily accessible[43a,c]. Decarboxylation to the corresponding ketones poses no problems.



In contrast, the 5-*endo*-trigonal cyclization **74**→**76** failed[43]; this is consistent with the Baldwin rules. The *O*-alkylated isomer **77** is the sole product. Perhaps the cationic center can interact stereoelectronically better with the lone electron pair at oxygen than with the π-system which is perpendicular to it (see **75**)[48]. Noteworthy is the observation that **78** gives smooth *C*-alkylation to form **79**. This case is different, since favored 5-*exo*-trigonal cyclization affording a product with the ketone function outside of the ring is involved[43a].

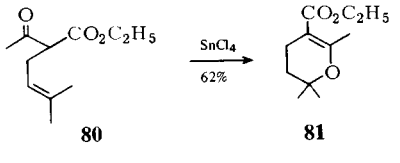


74 75 76 77

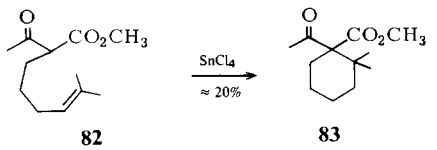


78 79

The limits of the method became clear during attempts to induce favored 4- and 6-*exo*-trigonal cyclizations of **80** and **82**, respectively[43]. In the former case only the *O*-alkylated product **81** was rapidly formed. On the other hand, the homolog **82** reacted very slowly, affording less than 20% of **83** after four days. Since large amounts of the starting material **82** remained unchanged, reversibility may be responsible.

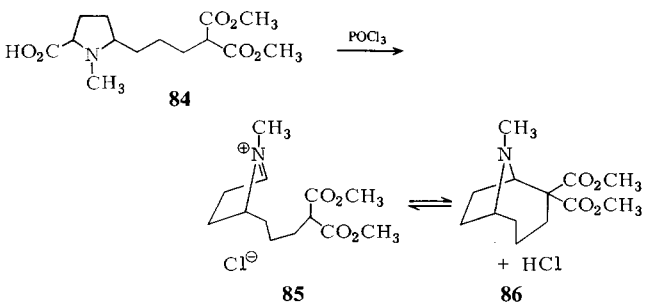


80 81



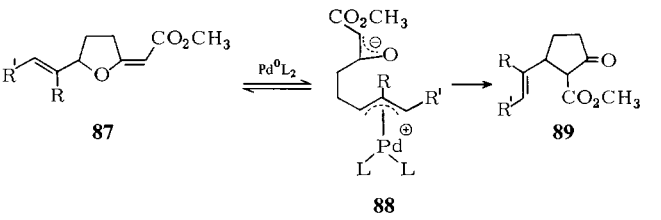
82 83

In this connection the observation made by *Rapoport et al.* is relevant, according to which the unfavorable position of the equilibrium **85** ⇌ **86** prevents useful yields of cyclization products[49a]. In other cases the regioselective cyclizations of alkylideneammonium salts discovered by these authors are essentially irreversible[49a]. Selenium-induced cyclizations of alkenyl-β-dicarbonyl compounds according to *Ley et al.* are also synthetically useful[49b]. Hg^{II}-salts generally effect intramolecular *O*-alkylation, although C—C bond formation predominates in certain cases[49c]. *Corey et al.* made use of the latter in their synthesis of (±)-aphidicolin[49c].



84 85 86

Although one must count with reversibility in $SnCl_4$ promoted cyclizations, it has not yet been possible to isomerize such *O*-alkylated products as **77** or **81** to the *C*-derivatives[43c]. Related and synthetically important processes are based on Pd^0-catalysis as reported recently by *Trost et al.*[50]. These processes are restricted to allyl systems, *e.g.*, **87**→**88**→**89**.

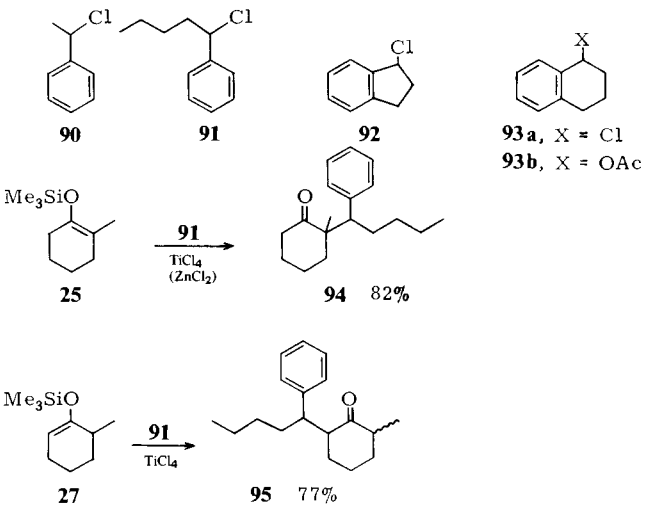


87 88 89

3. α-*sec*-Alkylation of Ketones and Carboxylic Acid Esters

As already stressed, conventional enolate chemistry is often of little use in the case of secondary alkyl halides, since elimination and loss of regiospecificity dominate. We therefore attempted to extend the concept of α-*tert*-alkylation to secondary alkyl halides. It turned out that the parent compound, isopropyl bromide, *fails* to alkylate silyl enol ethers of ketones in the presence of $TiCl_4$, since it is not S_N1 active enough[51]. The same applies to isopropyl iodide in the presence of silylated ketene ketals and ZnX_2[51].

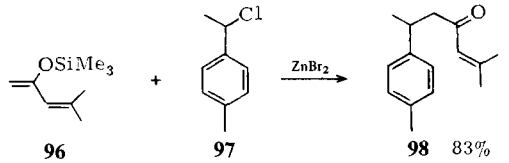
In sharp contrast, aryl-activated secondary alkyl halides such as **90**—**93** undergo smooth $TiCl_4$- or ZnX_2-induced α-alkylations[9,10,52]. We have demonstrated regiospecificity, *e.g.*, **25**→**94** and **27**→**95**. This, as well as the lack of polyalkylation underline the value of the method. In stereochemically relevant cases mixtures of diastereomers result. An application in the field of terpene chemistry is *Paterson*'s simple synthesis of tumerone **98**[52]. Surprisingly, activated secondary alkyl *acetates* can also be made to react at room temperature using ZnI_2 or $ZnBr_2$, *e.g.*, **99**+**93b**→**100**[18]. Also, carboxylic acid esters as well as acyloins are easily *sec*-alkylated as shown by the conversion of **21** into **101**[27]. Working with acetates is sometimes advantageous, since they are readily available and can be stored essentially indefinitely. Of course, they *cannot* be used in classical enolate chemistry, since they undergo *Claisen* condensation under the basic conditions.

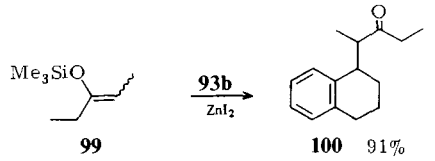


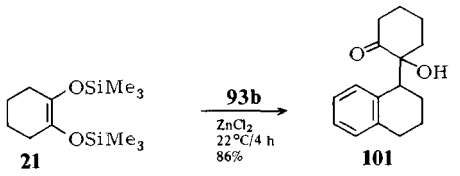
90 91 92 93a, X = Cl 93b, X = OAc

25 94 82%

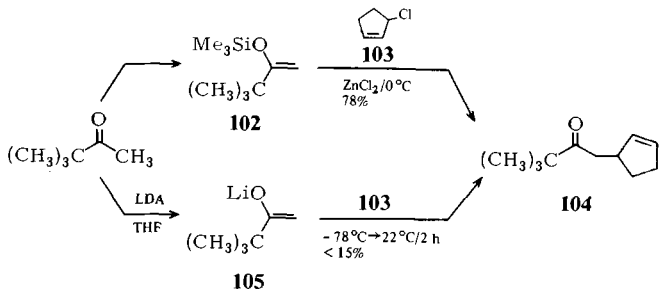
27 95 77%



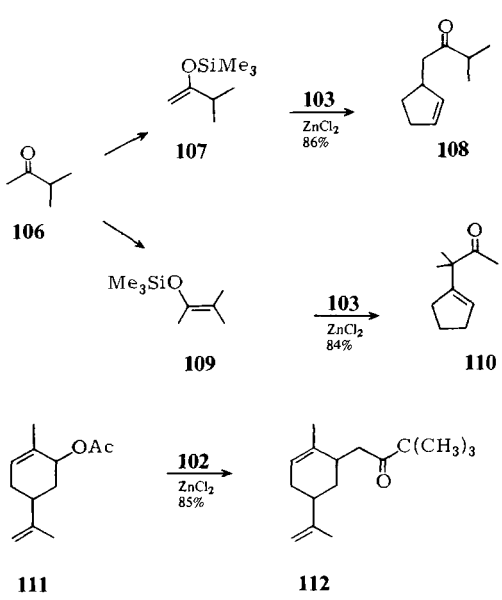




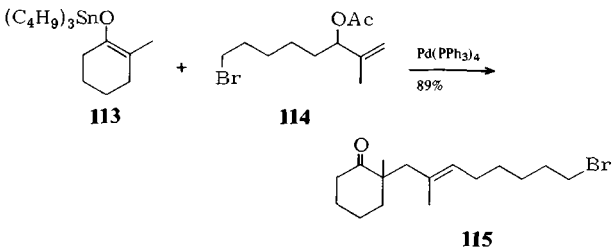
Secondary allyl halides and acetates are excellent reaction partners. The ZnX_2 induced reaction of **103** with a number of silyl enol ethers such as **102** occurs rapidly and essentially quantitatively under mild conditions without competing HCl-elimination[53]. The corresponding acetate



behaves analogously. In contrast, the very basic lithium enolate **105** derived from pinacolone affords less than 15% of the desired product **104**[53]! Complete regiospecificity in the reactions **107**→**108** and **109**→**110** is also impressive. The olefinic double bonds in **108** and **110** are easily hydrogenated, so that regiospecific cyclopentylation is possible for the first time. Cyclohexenyl acetates (*e.g.*, carvyl acetate **111**) react analogously at 22°C. Racemization points to a carbonium ion mechanism[53]. Open-chain secondary allyl acetates such as 1-methylallyl acetate react in the presence of $ZnCl_2$ considerably slower. The latter attacks the silyl enol ether derived from cyclopentanone at 70°C (1 h) to form 2-(1-methylallyl)cyclopentanone to the extent of 60%[53b]. The difference in reactivity has to do with the fact that the corresponding allyl cation is stabilized by only *one* alkyl group.

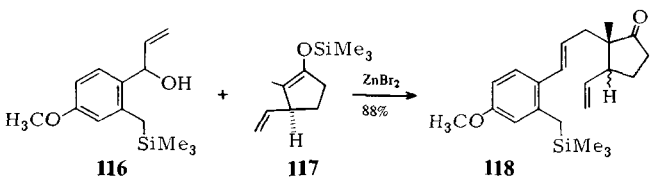


Excellent control of stereoselectivity in the use of allyl acetates as alkylating agents is possible *via* the corresponding π-Pd-complexes according to *Trost*'s general method[54a]. Although soft nucleophiles such as the anions of malonic acid esters are usually employed, stannyl enol ethers derived from ketones are also reactive **(113+114→115)**[54b]. The latter methodology is beset with problems, since stannyl enol ethers are not always easily



accessible, and the actual alkylation is not regiospecific in all cases[54b]. It has recently been reported that under certain conditions hard enolate anions participate in Pd-induced allylations[54c].

Secondary benzyl or allyl *alcohols* generally lead to poor results in Lewis acid mediated alkylations of silyl enol ethers[53]. An interesting exception is exemplified by the unusually reactive alcohol **116**, which reacts with **117** regiospecifically to afford **118**[55]. The product consists of a 4:1 diastereomeric mixture in which hydrogen is *trans* to the methyl group. It was easily converted into 11-α-hydroxy-

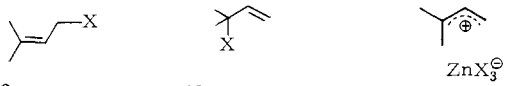


estrone methyl ether. The acetate of **116** is likely to behave similarly.

4. α-Prenylation of Ketones, Acyloins, Carboxylic Acid Esters and Lactones

Although prenyl halides **119a, b** are S_N2 reactive in enolate chemistry, they have not been used extensively[56]. Such possible problems as lack of regiospecifity or polyalkylation have not been investigated thoroughly[56]. In contrast, systematic studies relating to ZnX_2-induced prenylations have been performed[10,18,52,53]. All results using halides and acetates of the type **119a—c** and **120a, b** have

been positive to date. Since the assumption of intermediate ambident prenyl cations **121** is rather plausible, α-tertiary or α-primary alkylations can be expected.

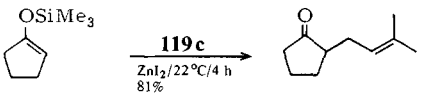


119a, X = Cl
119b, X = Br
119c, X = OAc

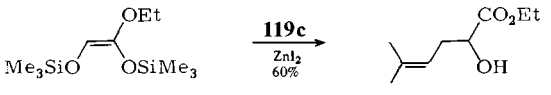
120a, X = Cl
120b, X = OAc

121

We have found that silyl enol ethers having tetrasubstituted double bonds undergo exclusive primary alkylation (prenylation)[10], as also reported by *Paterson*[52]. In all other cases up to 30–40% of isolable *tert*-alkylated compounds are formed[10]. The ratio of primary to tertiary attack is usually independent of the structure of the alkylating agent, since ZnX_2 induces rapid isomerization **120a**→**119a**. Thus, the discovery that the nature of the halogen attached to zinc affects the product ratio is synthetically important[10]. Whereas $ZnCl_2$ leads to appreciable amounts of *tert*-alkylated products, only traces are formed in case of ZnI_2; they are easily separated from the prenylated products during work-up. The same effect is observed if the less reactive CuI is used[10]. An even simpler prenylation procedure is the reaction of the easily accessible prenyl acetate **119c** or the isomer **120b** with silyl enol ethers in the presence of ZnI_2 at room temperature, *e.g.*, **122**→**123**[18]. The method is very mild, regiospecific, and does not yield undesired polyalkylation products. Other Lewis acids such as $TiCl_4$ or $SnCl_4$ lead to lower yields. Carboxylic acid esters[52,53], lactones[52] and acyloins[53] can also be prenylated *via* the silylated form, *e.g.*, **124**→**125**[53]. Application in terpene chemistry is likely to be successful. However, the yields in the case of geranyl acetate are disappointingly low (>30%)[53].

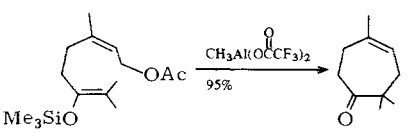


122 **123**



124 **125**

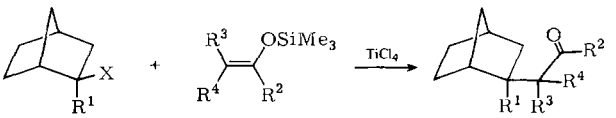
Intramolecular "prenylations" have also been carried out; *e.g.*, the methylaluminum bis(trifluoroacetate)-induced cyclization of the acetate **126** leading to karahanaenone **127** as described by *Nozaki et al.*[57]. This Lewis acid is made by treating trimethylaluminum with trifluoroacetic acid, and seems to be exceptionally mild. It results in higher yields than $AlCl_3$, Et_2AlCl, $TiCl_4$ or $SnCl_4$ (ZnX_2 was not tested in this case). The above process was also applied in other biomimetic cyclizations[57]. Pd(0)-induced intramolecular allylations involving anionized active methylene groups as acceptors are also known[58].



126 **127**

5. Anchimerically Accelerated Alkylations

Anchimeric assistance is another phenomenon which is known to increase S_N1 activity during solvolysis[59]. Since the solvent often displaces the neighboring group in the step which follows, retention of configuration results. We therefore posed the question whether "solvolytic" reactions with silyl enol ethers are possible in which the new C—C bond is formed stereoselectively with retention of configuration[60]. Indeed, *exo*-2-norbornyl bromide **128a** reacts with equivalent amounts of various silyl enol ethers **129** to form *exo* products **130** exclusively (Table 1). The tertiary alkyl chloride **128b** also gives only *exo* compounds[60]. Since the corresponding tertiary carbocation is classical, steric factors are responsible.



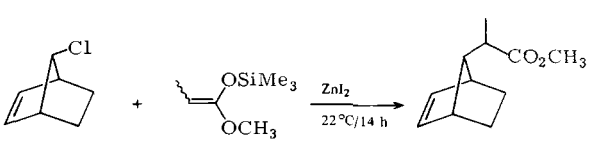
128a, R^1 = H, X = Br
128b, R^1 = CH_3, X = Cl

129 **130**

Table 1. α-Norbornylation of ketones to **130** [60].

Alkylating Agent	R^1	R^2	R^3	R^4	Yield of **130** [%]
128a	H	C_2H_5	CH_3	H	40
128a	H	$C(CH_3)_3$	H	H	73
128a	H	$CH_2C(CH_3)_3$	H	H	48
128a	H	$CH(CH_3)_2$	CH_3	CH_3	61
128b	CH_3	C_2H_5	CH_3	H	90
128b	CH_3	$C(CH_3)_3$	H	H	66
128b	CH_3	—$(CH_2)_3$—		H	65
128b	CH_3	—$(CH_2)_4$—		H	78

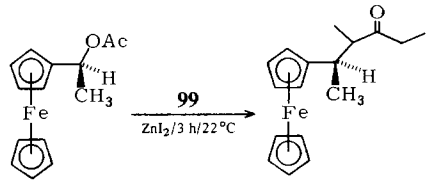
A widely quoted example for the drastic increase in solvolytic rate based on anchimeric assistance by a double bond pertains to *anti*-7-chloro-norbornene **131**[59]. A nonclassical carbocation as the reactive intermediate is generally postulated, which is attacked stereoselectively from the *anti* side by the solvent. The expectation that **131** reacts with silyl enol ethers with retention of configuration was fulfilled[60]. The best results were obtained using ZnI_2 at room temperature. Acyclic ketones as well as carboxylic acid esters are easily α-norbornenylated (*e.g.*, **132**→**133**), but not cyclic ketones[61]. The method is potentially useful, because oxidative cleavage of the double bond in the products (*e.g.*, **133**) yields trisubstituted cyclopentane derivatives with complete control of relative stereochemistry[60].



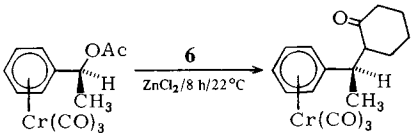
131 **132** **133** 95%

Obviously the above α-alkylations cannot be performed using classical enolate anions or nitrogen analogs. Therefore, the methods are complementary, as in most of the previously discussed cases. The broad spectrum of traditional carbonium ion chemistry contains many cases of neighboring group participation, so that the discovery of additional examples of anchimerically assisted alkylations is likely.

In more recent times unusually high solvolytic rates of certain transition metal complexes of the type **134** and **136** have been found[62]. This has to do with the fact that the



134 **135** 89%



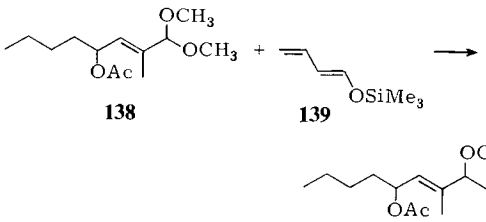
136 **137** 68%

carbocations being generated are significantly stabilized by the presence of the metal[62]. We have therefore initiated systematic studies concerning the use of **134** and **136** as alkylating agents. Indeed, the concept of S_N1 activity in Lewis acid promoted alkylations again proved to be useful as shown by the smooth reactions with **99** and **6**, respectively[63]. Whereas in the ferrocene derivative **134** both $ZnCl_2$ and ZnI_2 can be used as the catalyst, ZnI_2 fails in the case of **136** because it induces cleavage of chromium[63]. These α-alkylations are not possible using enolate anions, since the corresponding chlorides are extremely base sensitive. Although stereochemical studies of these unusual C—C bond forming reactions have not been completed, retention of configuration is likely to prevail. In the case of the chromium compounds, the metal is particularly easily introduced and then cleaved at a later stage, so that interesting synthetic perspectives arise. The metal functions as a vehicle for stereoselective C—C bond formation. Relevant are reactions of cationic tricarbonyl(dienyl)iron complexes with such nucleophiles as soft enolate anions[64a] and silyl enol ethers[64b] as reported by *Pearson* and *Birch*. The synthetically rewarding reactions of silyl enol ethers with hexacarbonyl(propargyl)dicobalt cations are also related[64c].

6. α-Alkoxyalkylation

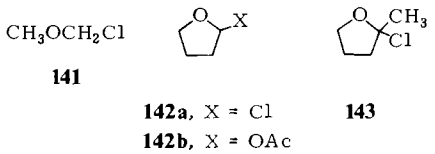
As already mentioned in the introduction, silyl enol ethers react with acetals in the presence of $TiCl_4$ to form β-alkoxyketones in a type of aldol addition[12]. If the system is particularly sensitive, a 1:1 mixture of $TiCl_4$ and $Ti[OCH(CH_3)_2]_4$ is recommended[12], which rapidly forms the milder Lewis acid $Cl_2Ti[OCH(CH_3)_2]_2$[65].

Thus, the reaction of **138** with **139** to form **140** is possible, which is a key intermediate in *Mukaiyama*'s total synthesis of variotin[66a]. Noteworthy is the γ-selectivity as well as the fact that the acetoxy group in the product **140** is not cleaved under the reaction conditions! The same principle was used in the synthesis of vitamin A[66b]. Similar reactions are catalyzed by trimethylsilyl trifluoromethanesulfonate as described by *Noyori et al.*[67]. Of prime importance is the observation that in this system C—C bond formation occurs diastereoselectively[67]. The reaction of 1,2-bis(trimethylsiloxy)cyclobutene with ketals in the presence of $TiCl_4$ or BF_3-ether is also useful, since the primary products are easily transformed into 2,2-dialkyl-1,3-cyclopentadiones[68]. Benzyloxymethylation of silyl enol ethers are of synthetic interest because hydrogenolysis of the products yields α-hydroxymethylketones[69a]. Finally, alkyl orthoformates likewise undergo Lewis acid promoted C—C bond formation with silyl enol ethers[12,69b].

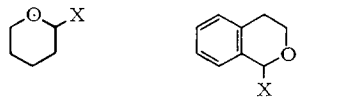


138 **139** **140**

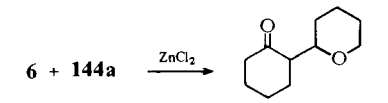
α-Alkoxyalkylation of enolate anions using α-chloroethers is possible in certain cases, *e.g.*, in the case of soft anions as are present in sodium-malonic acid diester[70]. Not much is known concerning analogous reactions of the more basic enolate anions of non-activated ketones or al-



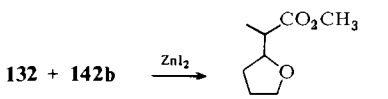
141 **142a**, X = Cl **143**
142b, X = OAc



144a, X = Cl **145a**, X = Br
144b, X = OAc **145b**, X = OAc



146 81%



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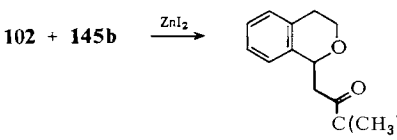
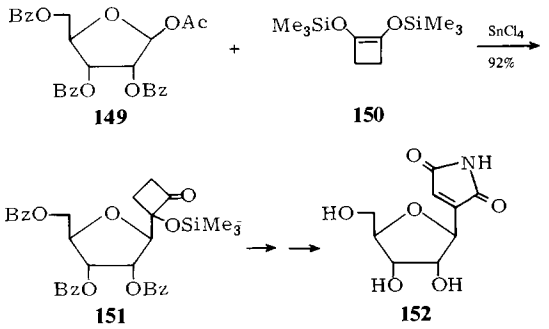


148 83%

dehydes. In these cases Lewis acid catalyzed α-alkylation seems to be the method of choice, since the α-chloroethers are extremely S_N1 active. Besides the parent compound **141**[52,71], cyclic α-chloroethers **142—145** also undergo smooth $ZnCl_2$-catalyzed α-alkoxyalkylations[72]. We were able to prove that the reactions are regiospecific. Worthy of note is the observation that the corresponding acetates **142b, 144b** and **145b** behave analogously[72]. Whereas the chlorides react rapidly at −20 °C (1—2 h) using catalytic amounts of ZnX_2, the acetates require room temperature (4—6 h). Interestingly, the usual dichloromethane can be replaced by ether. The latter dissolves zinc halides and ensures homogeneous catalysis. The reactions leading to **146—148** are typical for this mild alkylation procedure[72].

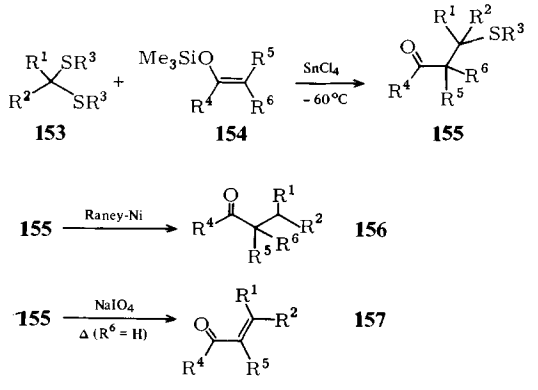
The above reaction type should have application in carbohydrate chemistry, particularly in the synthesis of *C*-substituted compounds. Indeed, a related $SnCl_4$-induced reaction between the protected β-D-ribose derivative **149** and the bis-silylated acyloin **150** was successful[73a]. The product **151** was converted in four additional steps into the antibiotic showdomycin **152.** Inspite of the fact that *Hanessian et al.* had already reported similar reactions[73b],



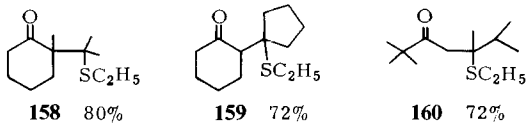
it is not clear whether the process can be carried out with other sugars in a general way (Bz = benzoyl).

7. α-Thioalkylation

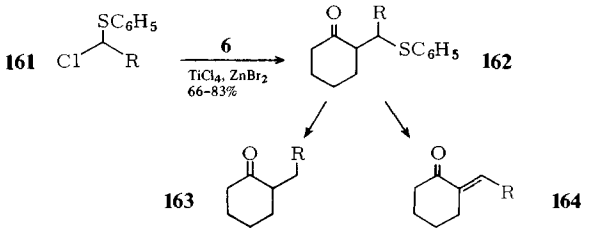
A synthetically interesting reaction is the Lewis acid induced α-thioalkylation of silyl enol ethers **154** with thioketals **153** to form **155.** Even upon varying the R groups considerably, we were able to obtain yields of 65—80%[10,74]. Furthermore, this thioalkylation is regiospecific. Whereas $FeCl_3$ was originally used as a thiophilic Lewis acid[10], $SnCl_4$ later turned out to be most effective[74].



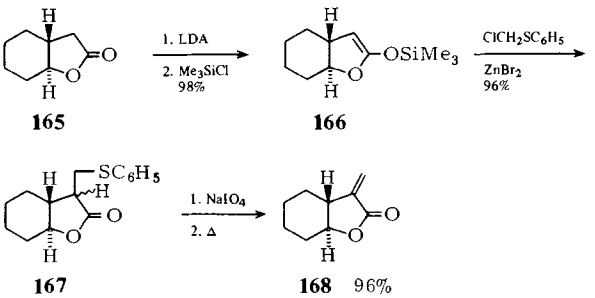
The value of the method lies in the fact that the products **155** can be treated with Raney Nickel to form **156,** or, in the case of $R^6 = H$, oxidatively converted into α,β-unsaturated carbonyl compounds **157.** In the former case the two-step sequence is equivalent to regiospecific α-*sec*-alkylation. The directed introduction of secondary alkyl groups in the α- *and* α′-position of unsymmetrical thioketals was previously not possible using conventional methods[1]. It is worthwhile to note that cyclic as well as branched groups can be introduced. In case of oxidative work-up, the sequence is equivalent to crossed aldol condensation, since both components **153** and **154** are derived from ketones. **158—160** serve as typical examples.



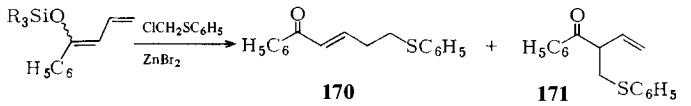
Thioalkylations using α-chlorothioethers **161** have been reported by *Paterson* and *Fleming*[75]. The products can be worked up reductively or oxidatively as described above, *e.g.*, **162→163** or **162→164**[75c]. In contrast to the previous reactions with thioketals, this sequence enables the intro-



duction of *primary* alkyl groups. Regiospecific methylation is thus possible[75b]. Based on the same principle, methenylation has been realized, *e.g.*, **165→168**[75a]. Parenthetically, lithium enolates derived from lactones give poor yields of thioalkylated products using $C_6H_5SCH_2I$, CH_3SCH_2Cl, CH_3SCH_2I or $C_6H_5CH_2SCH_2Br$[75a]. The $ZnBr_2$-induced thiomethylation is likely to be of use in the synthesis of certain cytotoxic sesquiterpene lactones such as vernolepin, helenalin or elephantin[76].



An interesting way to influence the α,γ-ratio in the alkylation of silyl dienol ethers is to vary the groups at silicon[77]. Upon substituting methyl by phenyl groups, the percentage of γ-alkylation increases. For example, thiomethylation of **169a** and **169b** gives rise to **170** and **171** in the ratios of 45 : 55 and 85 : 15, respectively. However, the

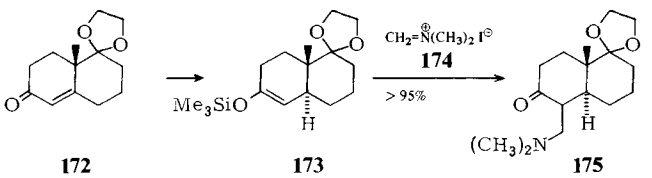


169a, R = CH_3
169b, R = C_6H_5

yields in the synthesis of silyl enol ethers are not always good[77].

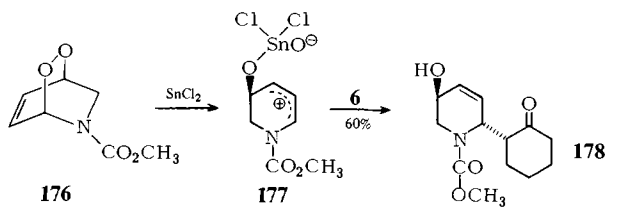
8. α-Aminoalkylation

According to *Danishefsky et al.*, silyl enol ethers, *e.g.* **173**, react with methyleneammonium salt **174** in the absence of Lewis acids[78a]. This reaction has also been observed with lithium[78b] or boron enolates[78c]. At higher temperatures even ketones and aldehydes themselves react[78d]. The Mannich bases can be transformed into α-methylenecarbonyl compounds in two steps, as in the synthesis of vernolepin[78a].



172 **173** **175**

Besides older α-aminoalkylation methods[70,79], more recent procedures[80a], in particular intramolecular cationic processes have been described which are exceedingly useful in the synthesis of alkaloids[49,80b]. An unusual α-aminoalkylation is based upon reductive cleavage of the peroxide bridge in **176** with the aid of $SnCl_2$[81]. The intermediate amino-stabilized allyl cation **177** reacts regio- and stereoselectively with **6** at the α-position to form **178.** This method has application in the field of alkaloid chemistry[81].

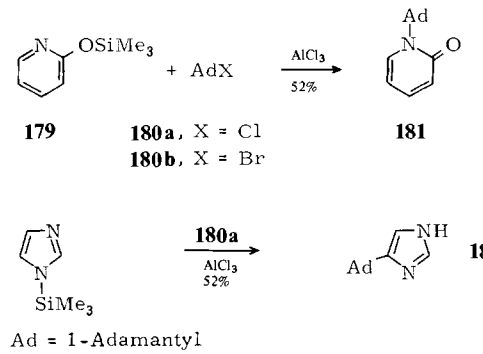


176 **177** **178**

9. Alkylation of Heterocycles

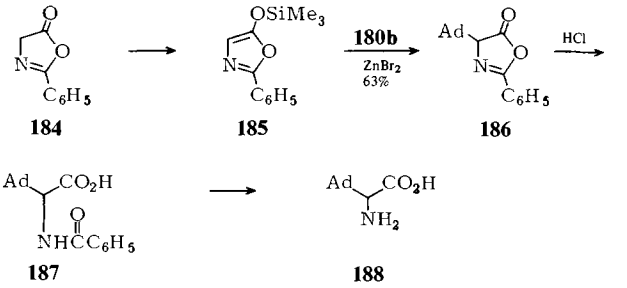
Not much is known concerning Lewis acid induced *C*-alkylation of *O*- or *N*-silylated heterocycles. For example, **179** reacts with **180a** not at carbon, but at nitrogen to form **181**[82]. *N*-Trimethylsilylimidazole **182** is selectively alkylated at carbon, since **183** is the only product isolated[82].

$ZnBr_2$-induced *C*-alkylations of the *O*-silyl derivative **185**[83] of the oxazolinone **184** are promising[84]. For example, **185** reacts smoothly with adamantyl bromide **180b** to form **186**[84]. Under acidic conditions the latter can be cleaved to **187** which is a precursor of **188.** In a formal sense glycine has been α-adamantylated. Other amino acids as well as acylamino ketones are also accessible *via* this route. It should be mentioned that under weakly basic conditions **184** reacts readily with S_N2 active alkylating agents, thereby providing the basis for some interesting chemistry as reported by *Steglich et al.*[85a]. These authors have also described a general sequence for the synthesis of amino acids having bulky groups at the α-position[85b]. However, it cannot be used for the introduction of polycyclic residues such as the adamantyl group.



179 **180a**, X = Cl; **180b**, X = Br **181**

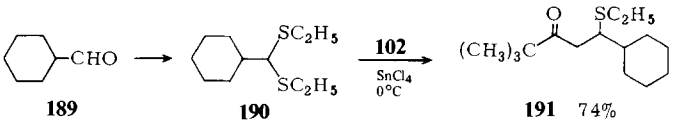
Ad = 1-Adamantyl



184 **185** **186** **187** **188**

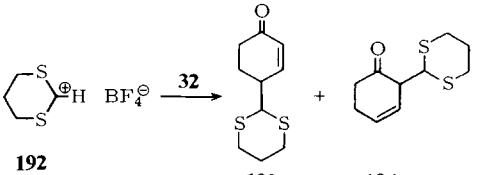
10. Summary and Future Work

During the short time between submission and correction of this review, several new aspects have appeared in the literature. The regiospecific thioalkylation using thioketals can be easily extended to thioacetals. Yields of 65—85% are common; an example is the synthesis of **191**[72]. This type of C—C bond formation is equivalent to that observed using primary α-chlorothioethers (*e.g.*, **161→162**)[75,86]. The only difference lies in the fact that in the new procedure stable thioacetals, easily obtained from aldehydes, are used as alkylating agents.



189 **190** **191** 74%

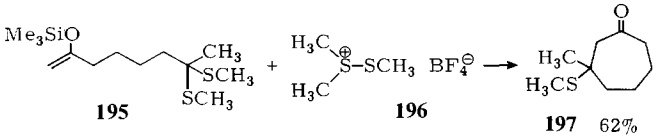
Thioalkylation of silyl enol ethers is also possible using 1,3-dithienium tetrafluoroborate **192**[87a]. Remarkably, silyl dienol ethers are alkylated regioselectively at the γ-position[87b], *e.g.*, **192+32→193.** Similar reactions have been carried out with 2-ethoxy-1,3-dithiolane[88].



192 **193** **194**

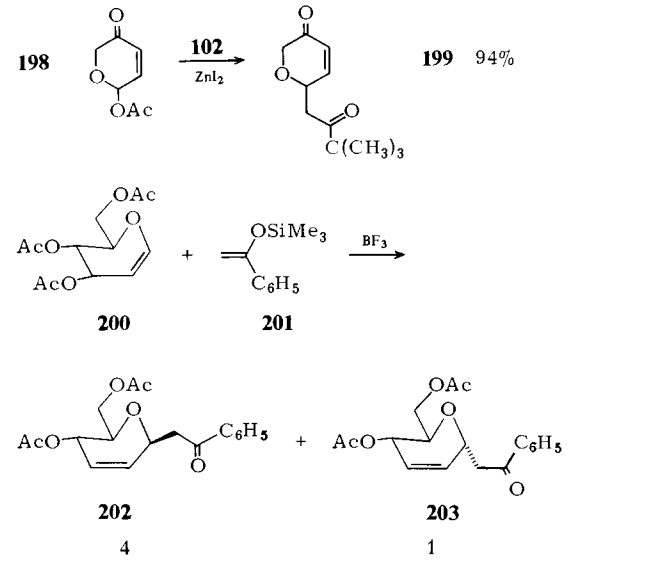
95 : 5

Intramolecular thioalkylations involving silyl enol ethers to form five-, six- and seven-membered rings are possible with dimethyl(methylthio)sulfonium tetrafluoroborate **196**, but not with such common Lewis acids as $SnCl_4$ or BF_3, *e.g.*, **195**→**197**[89].



195 **196** **197** 62%

Advances have also been made in the field of carbohydrate chemistry. Deoxyenonepyranosides of the type **198** react regioselectively with silyl enol ethers (*e.g.*, **102**→**199**)[72]. Closely related is the elegant reaction **200**→**202**[90].



198 **199** 94%

200 **201**

202 **203**

4 1

During the last four years the concept of Lewis acid-induced α-alkylations of *O*-silylated carbonyl compounds with S_N1 active alkylating agents has emerged as a powerful tool in synthetic organic chemistry. It was developed systematically in order to make that type of C—C bond formation amenable, which is not possible using classical enolate chemistry. Among others the long pending problem of α-*tert*-alkylation of carbonyl compounds was solved. Despite the fact that most of the reactions described in this review occur under mild conditions, generally show regiospecificity, and do not afford undesired polyalkylated products, some problems remain unexplored. Mechanistic aspects are currently unclear, in particular with respect to the Lewis acid. Radical processes appear likely in certain cases[16,35]. Also, the possible influence of the nature of the Lewis acid on diastereoselectivity during C—C bond formation has not been studied systematically. Finally, potential enantioselectivity in reactions of silyl enol ethers having chirally modified silyl groups ought to be considered. The same applies to the use of chiral Lewis acids.

I would like to thank my coworkers who have skillfully explored a number of reactions described in this review. Support by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

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Problems of Economic Exploitation of Basic Research Findings (Discoveries, Inventions, Patents, Licenses)**

By Friedrich-Karl Beier*

In spite of high expenditures for basic research and its indisputable significance for technological development, the knowledge so gained seldom finds its way into industrial practice without difficulty and undue delay. Even without changing the aims of basic research, more commercially exploitable research results will be obtained in the future. It is in the interests of the public and the scientists themselves that such results, not only broaden scientific knowledge, but also be transferred in the best possible way into innovative practice. An intensified patent and license policy for scientists' inventions is a more appropriate solution to this effect than any independent legal protection for scientific discoveries.

1. Introduction

The evolution of genetic engineering during the last few years is perhaps the most impressive example of the extraordinary significance which the results of basic research hold, not just for scientific, but for the technical, economic and social progress in our society. Emanating from the basic findings of molecular biology of the 1950's and 1960's, genetic science and engineering have today already reached a position where multifarious and important applications in medicine, agriculture, and engineering can be expected in the immediate and longer-range future. Human insulin, interferon, new vaccines against viruses and pathogens, genetically manipulated microorganisms for the manufacture of hormones and antibiotics, simplified and improved methods for cultivating plants and breeding animals, ethylene conversion, and manufacture of ethyl alcohol with the help of genetically altered bacteria; these are only some key words for applications, more or less near-at-hand - a list which could easily be extended.

Reports in newspapers and scientific publications give evidence of initiatives in the area of genetic engineering which leading scientists in the USA, Switzerland, and France have taken in order to convert their findings into industrial practice. To this end, they have not only succeeded in getting patents and offering them for licensed commercialization to the largest firms in the pharmaceutical and chemical industries, but have taken matters into their own hands by establishing their own development and production companies[1]. That these initiatives, uncustomary for scientists, might have good chances of economic success is perhaps best illustrated by the fact that the stock market value of the first four companies established with relatively modest means, namely, Citus, Genentech, Genex, and Biogen was already around 225 million dollars at the end of 1979[2].

2. The Problem

This development gives us occasion to reflect, more generally, upon what should be done in the future with the results of basic research, the discoveries and new findings brought forth in research institutes of universities and other research establishments, and indeed, not only in the area of biochemical research.

Should science be concerned only about *scientific* progress or also about *technical* progress, *i.e.*, about the transfer of scientific knowledge into technology, and then also, about the reduction of such technology to practice, through the acquisition of patent protection and licensing? Putting it somewhat provocatively, should scientists confine themselves to their primary role as researchers, publishing their research results and being content with scientific recognition and their salary, or should they—not only occasionally but in all promising cases which come along—also become *inventors*, develop their findings into useful industrial inventions, apply for patents and exploit these by granting licenses?

The question is multi-faceted and does not allow for a general answer. It holds not only many, still unresolved problems of a legal and organizational kind, but at the same time, touches on basic questions of science and research policy, *i.e.* the way in which a scientist sees his role, basic *versus* applied research, the relationship of science to the state, economy and business, and finally, questions of financing and organizing research. These questions cannot be discussed at length in this article, which will concentrate on the following general question: should scientists involved with basic research pay more attention to the economic exploitation of their own research results, and should their research organizations pursue a stronger patent and license policy?

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3. The Role of Basic Research[3]

To answer the question affirmatively does not mean changing the aims and functions of basic research, which must continue to be directed primarily to the acquisition of new scientific knowledge. Reducing results of basic research to practice does not mean that the emphasis should be shifted to applied research, which aims directly at the practical, industrial application of its results. That would be a fatal mistake. This emphasis on basic research is based neither on an elitist view of science nor on a lack of understanding by scientists of the so-called "social relevance" of their work. On the contrary, even if one assesses the value of research only by its economic and social returns, basic research as carried out in universities and other research institutions such as the Max-Planck-Gesellschaft (MPG) or the Centre National de la Recherche Scientifique (CNRS) has become more important than ever[4]. Today, basic innovations clearly promoting technical, economic and social progress cannot be realized without a basis in new scientific findings. In most cases, these findings can be brought forth only through systematic, long-term basic research, which is normally very expensive and full of risks. It may well be said that the more open the formulation of the problem, the more numerous the alternatives explored, the less one has of a specific practical result in sight from the beginning, and the greater the consequent risk for success, then the greater is the likelihood that something really basic emerges[5].

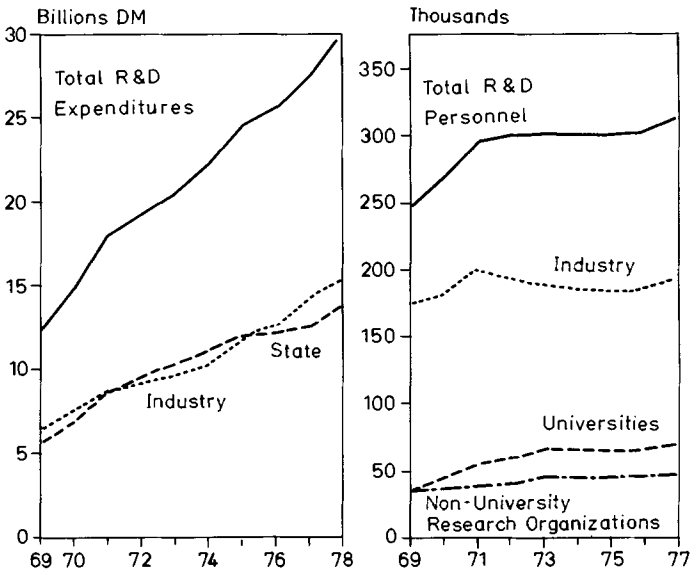

Fig. 1. Left: R & D expenditures in the Federal Republic of Germany 1969 to 1978. Right: Personnel in R & D research according to sectors 1969 to 1978 (source: BMFT, Stat. Bundesamt, Stifterverband, Wissenschaftsrat).

Table 1. Total budget for research and development in the Federal Republic of Germany, 1978 (Source: Stifterverband für die Deutsche Wissenschaft).

Financing / Carried out in	Republic [a] Total Mio DM	%	Fed. Mio DM	States [c] Mio DM	Industry Mio DM	%	Others [b] Mio DM	Total Mio DM	%
Industry	3650	25.7	3600	50	15096	98.4	520	19266	63.7
Universities	5185	36.6	935 [e]	4250	100	0.7	—	5285	17.4
Non-university Research organizations [d]	5350	37.7	4010	1340	140	0.9	360	5850	19.2
Total	14185	100	8545	5640	15336	100	880	30401	100
Total %	46.7	—	28.1	18.6	50.4	—	2.9	100	—

[a] Divided according to Federal government and States (including municipalities); in part, estimated figures. [b] Including private domestic institutions (PNP) and foreign countries. [c] Including municipalities. [d] Non-university research organizations include state organizations (Federal- and State-owned scientific organizations), private non-profit institutions (*e.g.*, major research organizations, Max-Planck-Gesellschaft) and foreign countries (*e.g.*, international research organizations). [e] Inclusive of estimated R & D portions in the financing of university construction, of 285 Million DM.

In industry, without governmental support, only large firms are in a position to carry out such research, and even they must concentrate primarily on areas of R & D which offer at least some prospects for commercial exploitation. The remaining industry, if it is carrying out not only development but also research, necessarily orients its research objectives to the immediate and short-term demands of the market for new products and processes. It must recover its R & D outlays within a foreseeable time, and therefore cannot, as a rule, even if it has great financial strength, conduct longer-term, high-risk projects. Basic research in universities and non-university research organizations must fill this gap.

Table 1 and Figure 1 present information about the distribution of total R & D expenditures for industrial and non-industrial research in university and other research organizations, which also provides an approximate indication of expenditures for basic research.

This division of functions is perfectly sensible, and it is therefore necessary[6] for the universities and research organizations to continue to concentrate on what others cannot do; namely, to carry out the laborious work of basic research, to which also belongs such long-term research projects as are carried out in the field of nuclear and plasma physics in the Garching, Karlsruhe, and Jülich research centers. It is also essential that the government (*i.e.*, the general public as taxpayers) finance this type of research.

4. Reasons for an Intensified Patent- und License Policy for Science

If this division of functions is in principle sensible, why then should scientists concern themselves with the exploitation of their research results, and to this end, engage in activities essentially alien to scientific research, such as the acquisition of patent protection and the granting of licenses? For this there is a series of reasons. These were

thoroughly discussed some time ago by a group of experts in the German Federal Ministry for Research and Technology (Bundesministerium für Forschung und Technologie—BMFT), and made the object of recommendations[7]. Shortly thereafter, this discussion was continued with scientists in a colloquium of the Max-Planck-Gesellschaft in Munich[8].

The results of these deliberations clearly run in the direction of an intensified patent and license policy in the area of publicly supported research, including basic research[9]. The main reasons for this may be summarized as follows:

4.1. Public Interest

1. The public not only has an interest that basic research be carried out, but also that its results, the new scientific findings, be put into technical, medical, and economic practice to thereby directly benefit the general public. In other words, the public is interested not only in scientific progress but, at the same time, in technical, economic, and social progress.

2. Scientific findings which have an economic use, or at least form the basis for it, are accruing today not only in industrial and applied research, but also in basic research. The most prominent example in Germany is the Max-Planck-Institut für Kohlenforschung in Mühlheim, which is today still fully self-financing from license revenues which are based on the fundamental discoveries of *Karl Ziegler* in the 1950's. But in many other areas also, in metal and semiconductor research, cultivation and breeding research, plasma physics, biochemical and biophysical research, many new and exploitable findings are constantly being made. The range of possible inventions from basic research institutes is large: from new chemical compounds, amalgams, pharmaceuticals, vaccines, plant cultivation and animal breeding, physical-technical manufacturing methods and analysis and measurement methods, to scientific devices and instruments.

3. The conversion of basic research results into new, economically usable products and procedures does not take place by itself, but *requires active participation from all who are involved in this innovative process* from the basic researcher to the development engineer, to the patent attorney, to the entrepreneur and the marketing specialist. A look at Figure 2 indicates that this process is lengthy, tiresome, and susceptible to problems.

The innovation process comprises the three main stages of *research, development* and *application,* and is only completed when, from the scientific findings gained in the research stage, an economically usable invention is developed in the invention and development stages, and when the object of this invention, the new product, is not only manufactured in the application stage, but also made available to a sufficient number of consumers in the market place. Only then, has scientific progress achieved, *via* the way of technical progress, finally economic and social progress.

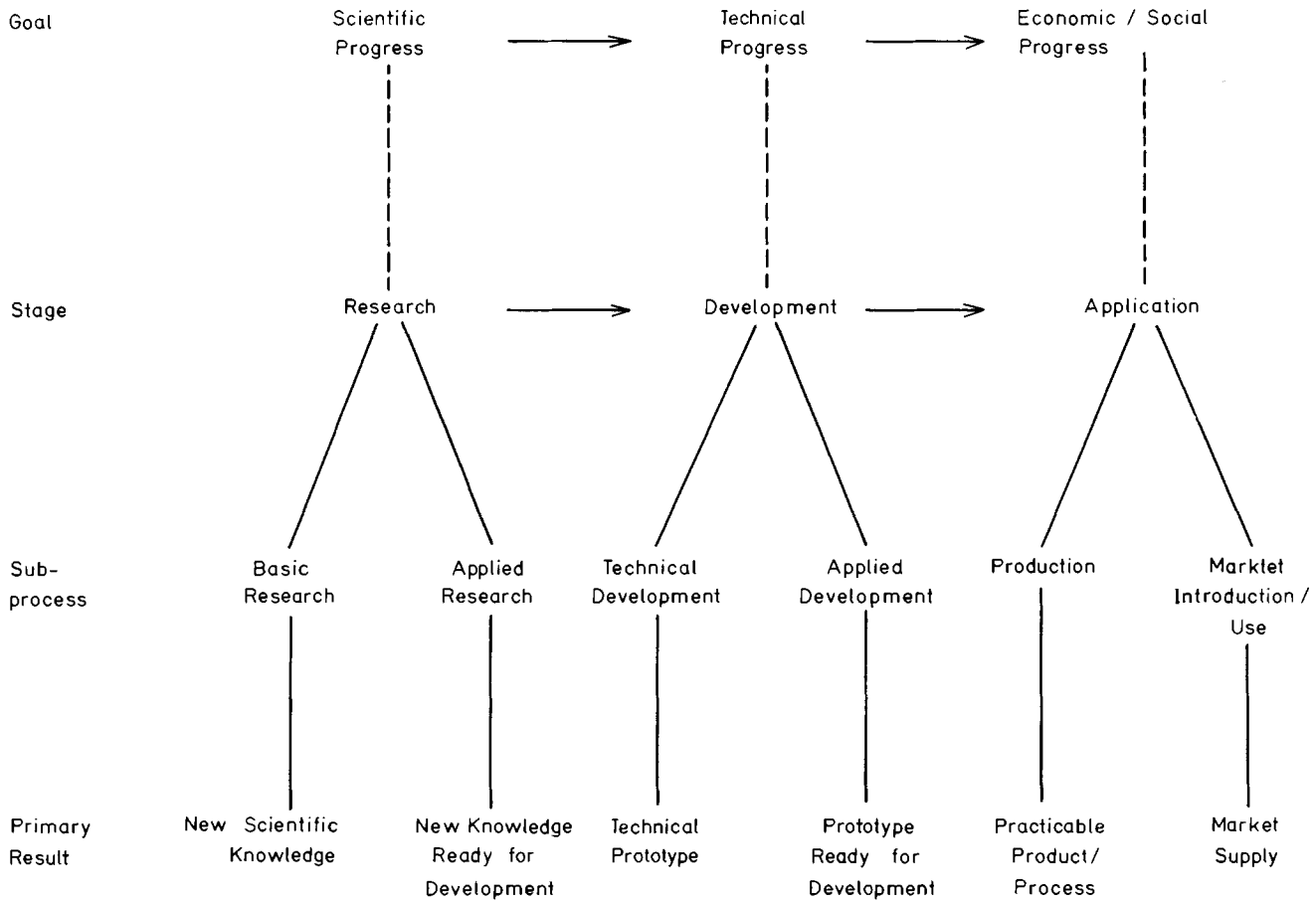

Fig. 2. Subdivision of the innovation process.

4. In fact, this process of reducing research results to practice functions either not at all or only imperfectly, if scientists, especially the basic researchers standing at the beginning of the chain of innovation, confine themselves to producing new scientific knowledge and making it available through reports and publications to the scientific community. This might promote scientific progress, but technical and economic progress are advanced only indirectly and with long time delays.

One would think that the best way of transferring knowledge into practical use is to publish new findings for everyone's free use, and that this method is even the most adequate in the field of publically financed research. But, the experience gained not only in the Federal Republic of Germany, but also in other countries, with such methods of imparting knowledge is definitely negative[10].

5. There are, above all, three reasons for this: a) scientific literature has only minimal value as a basis for investment decisions by industry; b) the published research results are as a rule still too far from industrial application, and hence, the development and market introduction risks too great; c) even in cases of research findings promising a successful technical and economic use, industry is not easily prepared to incorporate into its development and production programs such research results which have been made freely available through publication. No one is seriously interested in gratis technology, available equally to everyone, not only because man is inclined to doubt the value of a gift, but above all, because the recipient of this dubious gift, in which much more money must still be invested, is not alone in receiving it, but must participate with everyone else.

6. For this simple reason, it is essential, even in the area of publicly financed research, to combine the traditional publication policy with an intensified *patent and license policy*. Only this can ensure a satisfactory transfer of knowledge into practice. Industry is interested in research results only if they are patented or, at least, patentable, for patent protection assures the company a preferential position against its competitors which allows it to invest in the further development and market introduction[11]. The experience, including that of the Garching Instrumente GmbH, founded by the Max-Planck-Gesellschaft to exploit inventions made in research institutes, shows that inventions from government supported research can only be commerialized if patent protection is acquired and—in most cases—exclusive licenses are granted[12]. This was also the undisputed outcome of the debates within the BMFT (Federal Ministry for Research and Technology in the Federal Republic of Germany) group of experts and the Munich colloquium mentioned previously[13].

What can be done?

What then, does this call for a strengthened patent and license policy mean *for those scientists involved in basic research?*

1. Scientists should not be shy about developing their *"invent and patent" consciousness* somewhat more than they have hitherto. This requires above all, that they examine their findings for possible industrial applications, and indeed before results are published, as otherwise, later patent-protected exploitation is lost[14].

2. As to the *further development* of scientific knowledge to a patentable invention, two cases may be distinguished: a) If the development is drawn-out, expensive, or too far removed from the research objectives of the institute, it cannot in principle be the function of the individual scientists or their institutes to undertake by themselves such unfamiliar development activity. In cases having good prospects of commercial success, a development or cooperation contract should, be entered into with industry or appropriate institutes, with the help of state or private funds[15].—b) There is, however, an increasingly larger and more important area in which a scientific discovery is at the same time a patentable ivention, or may readily be developed into one without great expense (cf. Table 2). Gene research and technology on the one hand, plasma physics and nuclear engineering on the other, are examples of the fact that especially in promising areas, the traditional boundaries between basic and applied research, between discovery and invention, between pure science and engineering become more and more blurred, and progress in basic research cannot be achieved without advanced technology, and *vice versa*. A new microorganism with defined technical, pharmacological, or serological characteristics produced by a gene researcher with the help of gene technology, is at the same time a discovery and an invention, industrially applicable, and hence patentable[16]. Conversely, in plasma physics and other fields of basic research no progress can be achieved without self-developed technology—extensive, costly technology.

In my opinion, the patent and license policy of universities and other research organizations such as the Max-Planck-Gesellschaft should be aimed, above all, at such technical inventions which necessarily result from, or are needed for, basic research without additional development expenditures[17].

Table 2. Basic terms.

Discoveries	Inventions
Definition	Definition
Pure knowledge/finding of - laws of nature - pure theories - characteristics of nature - natural phenomenon	- solution directed to a specific problem - influence of natural forces
Protection	Protection
- patent law, no protection possibility - copyright law, protection of the form of presentation, not contents - trade secrets protection	- patent law - protection of plant varieties - trade secrets protection

3. In the case of a patentable invention with realistic prospects for exploitation, and where the scientist has the impression from his own knowledge of the state of technology or from a self-conducted search, that it relates to a new and not obvious invention, a *patent or utility model application* should be filed in every appropriate case, in order to secure priority and a basis for later commercialization.

In view of the increasing complexity of the filing and examination procedures, and the numerous possibilities for patent protection at the national, European and international levels[18], today less than ever, can one do without the expert advice of a patent attorney or patent agent experienced in patent and licensing matters, not the least, to save oneself needless clerical work and expenditures of time[19].

An important distinction is to be observed in the Federal Republic of Germany with respect to acquiring patent protection: professors, assistant professors, and academic assistants in universities are not governed by the provisions of the law on employee inventions of 1957; their research results are *independent inventions*, which they themselves can apply to protect and independently exploit. However, this so-called "academic's privilege" does not apply to the scientists working in the institutes of the Max-Planck-Gesellschaft, or Federal or state-owned research organizations. Their inventions, made in this capacity, are *employee inventions* which, according to the provisions of the employee invention law, the employer may claim as his property and apply to protect and exploit it. This right of the employer is, however, combined with the legal obligation to file a patent application for the employee's invention, and in cases where protectable, to pay the salaried inventor a reasonable compensation[20], which according to the rules for inventors in the Max-Planck-Gesellschaft, for example, amounts to 30% of the gross license receipts.

Which of these two routes is more advantagous for the scientist, and, which one ensures that research results are better reduced to practice, is still an unresolved question, and difficult to clarify because of the lack of safe data. The university researcher has more freedom to exploit his invention, and hence in theory, can obtain higher license revenues, but he bears the total and not insignificant costs of patenting, further development, and commercialization, and with that, the entire risk. All of this will normally be too much for him. In the face of these difficulties many professors completely refrain from economically exploiting their inventions. Others relinquish both the legal protection and the later commercialization completely to an industrial enterprise, provided they are successful in enjoying an actual interest in a given enterprise. Frequently, this presupposes that the academic inventor upholds close cooperation with certain enterprises, and is satisfied with a quite modest compensation, for his inventive efforts. Unlike in the USA, for instance, the German universities offer little assistance to their academic inventors in patenting and exploiting their inventions. On the contrary, the university administrations, and above all the Ministries of Education and Cultural Affairs in charge, view invention and the industrial activity of professors with suspicion, as an undesirable "activity on the side". Although of great economic value, the inventing and patenting activity of a teacher is viewed as an interference with his primary teaching obligations, which also endangers the standard salary structure. This is a most unsatisfactory situation[21].

The situation is different with inventions made by research done outside the universities. They are normally claimed by the employing research organization, *e.g.*, the Max-Planck-Gesellschaft, in accordance with the rules of the employee invention law. This not only increases the interest of the research organization in economic exploitation but also obliges the employer at the same time to apply for patent protection, to assume the entire costs, and to pay a reasonable compensation to the scientist in case of successful commercialization of the invention. The commercialization risk and the basically atypical legal-business activity of exploiting the invention are both taken away from the scientist.

To fulfil these tasks, the large state-owned research centers and the research organizations have set up their own patent departments. The Max-Planck-Gesellschaft has, in addition, created its own exploitation company, the Garching Instrumente GmbH, whose assisting functions are not restricted to inventions from the Max-Planck-Gesellschaft. In the first ten years of its existence, it was able to achieve not overwhelming, but certainly considerable, success in commercializing scientists' inventions[22].

4. Yet, even with the involvement of exploitation companies of this kind, the problem of putting research results into practice is only partially resolved. The road from a patentable invention to a successful product or process, from the inventing stage to the application stage, is often still long, and in most cases requires high investments for the necessary *further development and market introduction.* Prospective licensees from small and medium sized industrial organizations which for lack of their own research capacity, are especially interested in inventions from state supported research, need risk capital which should be made available to a considerably increased extent and in an unbureaucratic manner. The government bodies responsible for promoting research and economic affairs should devote stronger attention to this, as yet unresolved, question. For it goes without saying, that today it is more important than ever to make full use of the innovative potential available in our research institutions. The public has a vital interest in this.

4.2. The Interests of Science

Where, however, do the interests of the research organizations, research institutes and the individual scientist lie in an improved transfer of their research results into practice?

General Aspects

1. Probably every scientist should be interested, not only in having his research results noticed and discussed by his colleagues, but in having them find their way into technical, medical and industrial practice, and thereby to gain wider public recognition as a substantial creative contribution to technical and economic progress. The reputations of *Otto Hahn*, of *Adolf Butenandt*, and of *Karl Ziegler* have not been damaged as a result of these scholars having paid attention to the transfer of their discoveries into industrial practice, having worked together with industry, having made inventions, and having taken out patents[23].

2. Increased contacts between scientists and industry give both sides valuable encouragement and assistance in

their research and development activities. A welcome side-effect of these contacts is to improve the *mobility* of scientists, namely to facilitate the often difficult movement from positions in research to positions in industry, and *vice versa*. On the one hand industry offers scientists with a practical, inventive mind better career prospects than pure theorists. Because of the limited positions available in institutes, the institute should welcome every transfer to industry promoted by contact therewith, even if the loss of good assistants is sometimes painful. On the other hand a research scientist in industry will more readily accept a job in a university, if through prior contacts, he knows his future place of operation and can continue his inventive activity there.

3. Furthermore, a scientist can really have nothing against being named as inventor or co-inventor in a patent, and entering, with his technology-enriching accomplishment, the world-wide patent documentation system[24]. In this way, his discovery is not only extensively disseminated within industry and science, but the being named as inventor will also be regarded as a proof of quality and efficiency of his research endeavor.

4. Finally, one more important aspect: through an intensive invention, patent and license policy, science can, in a simple, understandable and effective way, demonstrate to the government, whose members are continuously asking what comes out of the research billions, just what service it renders the public. The talk about "ivory towers" in the scientific community could be dispelled more effectively than through verbal denials, if the public could more often be presented with a scientist's important invention, with all of its useful consequences for economic growth and social progress.

Financial Aspects

What financial benefit could be brought about for research institutes and the individual scientists by an intensified invention, patent and license activity?

1. First of all, a warning should be given against exaggerated expectations. It would be absolutely unrealistic to think that *e.g.*, the Max-Planck-Gesellschaft, could possibly ever finance its total expenses (annual budget 860 million DM), or even a considerable portion thereof, from its own license revenues. This much is not brought in, even by important inventions. Even if all research results which are industrially applicable could in future be recognized, patented and optimally commercialized as such, the income obtainable therefrom could at best make up only a small fraction of the total research budget. The Institut für Kohlenforschung in Mühlheim (Germany), which has been able to finance itself for decades from the *Ziegler* inventions, is a special and exceptional case that cannot be generalized[25]. Nevertheless, the Mühlheim example shows that economic exploitation of research results, if carried out in an expert way through licensing, can definitely be a rewarding business. Experience in the USA with the commercialization of university inventions, as well as the success to date of Garching Instrumente GmbH, also point in the same direction.

2. Even if no spectacular revenues can be expected, it is still worth taking the trouble in every appropriate case. We see that public funds for research are becoming ever tighter, and sufficient financing for research purposes can only be achieved through tough negotiations and through ever new concessions to the government. In such times, every single *additional* million of hard currency flowing into research must be highly welcomed, and must not be viewed as a negligible quantity.

3. The accent is on the word *additional*, and that means: license revenues from inventions are only of interest for the scientist if they do not lead to a corresponding reduction in the supporting funds from the government, but are freely available for additional research and development activities. Research could thereby win back some freedom and flexibility which it had at one time, which it needs, and which has been limited as a result of its ever stronger commitment to governmental budgetary rules. This greater *freedom of research* obtained through one's own initiative is in my opinion the most important reason, from the point of view of science, for a strengthened patent and license policy.

Legal Aspects

Finally, what is the situation regarding legal protection for scientific research results?

No Legal Protection for Discoveries

1. It undoubtedly contradicts the natural *sense of justice* that the inventor of a toothbrush or the composer of a pop song can obtain from their "creative" output by patent or copyright protection considerable incomes (the composer even until 50 or 70 years following his death), while the scientist who has made a basic discovery receives no legal protection for it and is consequently left empty-handed. He must continue to fight for the necessary research money from public or private donations, looking on as industry proceeds to make profitable inventions and a good business from his discovery.

2. This situation has frequently been deplored and has given rise to numerous suggestions to also give scientists and basic researchers an *exclusive right* to their discoveries, a "droit des savants" (scholars' right), or at any rate, to give them a share in the economic exploitation of their discoveries by way of an industry-fed pool of funds[26]. All of these demands and suggestions, which were thoroughly discussed in the League of Nations during the 1920's, and in UNESCO during the 1950's, never got off the ground, admittedly with good reason. They ignored the fact that scientific findings as such, which are still too far removed from economic utilization, cannot be made the subject of exclusive rights or claims for compensation, without unreasably hindering scientific and technical development.

3. We can therefore shelve all of these suggestions for independent legal protection for scientific discoveries, even if some socialist countries have introduced them, and recently, at the initiative of the Soviet Union, an international agreement for the registration of scientific discoveries was concluded in Geneva. This agreement provides no legal protection of any kind, only international registration for those scientific discoveries which are recognized as such in their country of origin. Accordingly, it is really ac-

ceptable only to countries such as the Soviet Union, where a state authority can decide what is a scientific discovery and who is its discoverer[27].

Inclusion of Discoveries in the System of Patent Protection

1. A better approach to the problem is to include the growing number of basic research findings, which are at the same time useful inventions or can be made such without significant development expenditures, into the traditional patent system. This is, even under the present state of the law, a possible and sensible solution. In the area of biochemical, biological, and largely also in the area of chemical-pharmaceutical research, patent protection is already available for new findings which are discoveries as well as inventions. A new microorganism or a new inorganic or organic compound, whose structure and characteristics have been clarified, is an invention for which patents will be granted (cf. Tables 2 and 3).

Table 3. Patent protection.

Patentable inventions
Definition
- Instruction of systematic technical action
- Application of controllable forces of nature
- Achievement of a result through foreseeable causal development
Criteria
- Novelty
• solution not known
• standard: state of the art at filing date
• novelty-defeating: other and own publications, oral disclosures, non-secret use
- Inventive step
• solution not obvious
• standard: entire state of the art, average skilled man in the art
- Industrial applicability
• suitability for industrial manufacture
• suitability for industrial utilization
Exceptions
- Discoveries
- Scientific theories
- Mathematical methods
- Computer programs
- Pure ideas and business rules
- Plant varieties (→plant variety protection) animal breeds (microorganism Patentable)
- Medical treatment methods
- Unlawful and immoral inventions

2. Although the patent laws of all countries, as well as the new European patent law, adhere to the traditional principle whereby discoveries and other scientific findings (Table 2) are excluded, as such, from patent protection, *more recent jurisprudential developments*, and indeed, precisely in the above-mentioned research fields, indicate a distinct trend towards advancing the threshold of patentability into the area of scientific discoveries, and therewith, basic research[28]. Judicial recognition of the protection of microorganisms, new plant varieties, the adoption of absolute product protection for chemical compounds, including natural substances, the patentability of intermediate chemical products, the possibility to file additional, or modify existing, descriptions of the technical, medical, or other fields of application of a chemical compound during the examination of a patent application (which means up to 10 years after the filing date)—all of these indicate the *on-going trend towards patent protection for basic research results.*

Protection Against One's Own Prior Publications

1. For attaining effective patent protection, one more step should be taken, namely, the re-introduction of a suitably long grace period for disclosures made by the scientist-inventor himself into the national and European patent laws, and if possible, on a world-wide basis[29]. According to the so-called absolute novelty concept, quite recently introduced and now in effect throughout the whole of Europe, patentability is excluded for any material disclosed by written or oral description, or by use, prior to the filing of the patent application, and it does not matter whether the disclosure comes from the inventor himself or a third party.

2. This severe rule is unbearable, not only for independent inventors and small and medium sized industry, but above all, for the scientist working in a research laboratory. It necessarily leads to a conflict between his legitimate and recognized interest in publishing his research results as soon as possible, and the interest in subsequent patent protection as a basic requirement for economic exploitation. This forces him to adopt a "wait and see" attitude with respect to publication, until he, or his institute's management, has investigated the economic relevance of the research results, and if warranted, a patent application has been filed. In some institutes with a developed patent consciousness, such an investigation is indeed undertaken as a matter of routine, just as in industry, without the publication being appreciably delayed. This is certainly possible and *de lege lata* important. But something important can so easily be overlooked, and then patent protection is lost once and for all[30]. The fact alone that important findings recognized as economically relevant must anxiously be kept secret from colleagues and visitors until a subsequent patent application, is embarrassing enough.

3. Only a six-month or even one year grace period for disclosures by the inventor himself, or his legal successor, such as for example, the USA and Japan recognize, and such as we had until recently in Germany, can bring relief to this situation. The scientist can then safely publish, and, after that, still has a half or a whole year's time to investigate the economic relevance of his new finding, and if worthy, to reflect on it and test it further in order to prepare and file, with expert help, a patent application. The publication or public use during the grace period defeats neither the novelty nor the inventive step required for the patent application subsequently filed by him or his legal successor.

At the present time, this topic is being debated with some prospects of success by national and international bodies concerned with legal protection of industrial property. But, a fairly long time will certainly pass until an appropriate change in the present German and European patent laws, which have only just come into effect, may be expected. Until then, if the scientist does not want to cut himself off from the possibility of economic exploitation of his research results, he has to live up to the unfortunate

maxim that he must not speak or write about his research results until the moment he has applied for patent protection.

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[1] Cf. N. Wade: "Recombinant DNA: Warming Up for the Big Payoff", *Science 206* (1979) 663; A. Ullrich: "Die Genentech-Story", *Nachr. Chem. Tech. Lab. 28* (1980) 727; D. Dickson: "More commercial genetic manipulation—Harvard and Biogen Establish Cambridge Labs", *Nature 287* (1980) 769; also, the report of the French Embassy in Washington, "Le génie génétique bactérien aux Etat Unis" ("The Genetic Engineering of Bacteria in the United States"), *Progr. Scientifique* no. 210 (1981) 29.

[2] Cf. N. Wade, "Gene Splicing Company Wows Wall Street", *Science 210* (1980) 506; also, the report "Die Gentechnologie öffnet Milliarden-Märkte" ("Genetic Engineering opens Billion Dollar Markets"), *Blick durch die Wirtschaft* No. 87 (1981) 7.

[3] Included thereunder is generally all research work which is exclusively directed to gaining new scientific knowledge, without being oriented predominantly toward the goal of practical application. Cf.: The Measurement of Scientific and Technical Activities ("Frascati Manual" 1980), OECD, Paris 1981, p. 25.

[4] The British Council for Scientific Policy (Second Report on Science Policy, London 1967, p. 12) aptly expressed this: „Basic research provides most of the original discoveries and hypothesis from which all other progress flows".

[5] An authority such as *Sir Ernst Chain* believes, for example, that his work on lysozyme and penicillin, which at the beginning did not have the slightest prospect for practical application, but whose later significance is generally known, could never have been carried out in a "mission-directed" institute in industry. Cf. E. Chain: "Entwicklung und gegenwärtiger Stand der antibakteriellen Antibiotikatherapie" ("Development and Present State of Antibiotic Therapy Against Bacteria"). Marburger Forum Philippinum 1975, pp. 25—26 (p. 30).

[6] Even large chemical companies which carry on much outstanding research in their own laboratories do not appear to ask this question. This year, Hoechst AG gave a notable research grant to the amount of 50 million dollars to Harvard University's Massachusetts General Hospital, for basic research in the area of genetic engineering. Cf. K. Done, P. Betts: "Hoechst Grants Harvard $ 50 m for Genetic Engineering Research", *Financial Times* May 22, 1981, p. 1; also, H. Pfaeffle: "Höchst schürt das Wettrennen in der Gen-Technik" ("Hoechst Stirs Up the Race in Genetic Engineering"), *Süddeutsche Zeitung* July 14, 1981, p. 17; D. Fishlock: "Hoechst braves home fury to invest abroad", *Financial Times*, Nov. 20, 1981, p. 10.

[7] Recommendations of the Group of Experts of the Federal Minister for Research and Technology, "Patente und Lizenzen bei öffentlich geförderter Forschung und Entwicklung" ("Patents and Licenses in Publicly-Supported Research and Development"), *GRUR* (Gewerblicher Rechtsschutz und Urheberrecht) *1978*, 349.

[8] Th. Bodewig: "Erfinder-, patent- und lizenzrechtliche Fragen der öffentlich geförderten Forschung" ("Legal Questions Concerning Inventors, Patents and Licenses in Publicly-Supported Research"), report on a colloquium of the Max-Planck-Gesellschaft, *GRUR Int.* (Gewerblicher Rechtsschutz und Urheberrecht, Internationaler Teil) *1980*, 597; abridged version in *Max-Planck-Gesellschaft-Spiegel 5/80*, 25.

[9] The development is also proceeding in a similar way in other industrial countries, as for example, in the USA and Great Britain. See, Government Patent Policy Study, Final Report by Harbridge-House, Inc. for the FCST-Committee on Government Patent Policy, Washington, D.C. (GPO) 1968; Smith: "Money for New Rope—The Industrial Exploitation of University Inventions", Part 1 (Ideas and Inventions), Part 2 (Development and Commercial Success), *European Intellectual Property Review*, December 1978, p. 11, January 1979, p. 2.

[10] Cf. F. K. Beier: "Die Bedeutung des Patentschutzes für den technischen, wirtschaftlichen und sozialen Fortschritt" ("The Significance of the Patent System for Technical, Economic and Social Progress"), *GRUR Int. 1979*, 227, 234; for more details, see Beier/Ullrich: Öffentlich geförderte Forschung und Patentschutz, 3 Volumes, Verlag Chemie, Weinheim 1982ff.

[11] According to the research agreements which the U. S. company, DuPont, has reached with Harvard University for basic research in the field of molecular biology, and also, according to the Hoechst/Harvard agreements, Harvard receives the patents resulting from the research work. However, DuPont and Hoechst are entitled to the exclusive rights to the exploitation of the patents, in return for which royalties become payable to Harvard. Cf. also [6].

[12] Cf. E. Guilino, *GRUR 1974*, 187.

[13] Cf. also [7, 8].

[14] What is responsible for this is the so-called absolute novelty concept recently introduced into the German and European patent laws, and the lack of a grace period for disclosures made by the inventor; for more details on this, see [28].

[15] The agreements with Harvard University are good examples of this; cf. also [6].

[16] In its "Chakrabarty" decision dated June 16, 1980, the U. S. Supreme Court stated that "living micro-organisms produced by man and as a result having characteristics not occurring in nature" are patentable. German translation is in *GRUR Int. 1980*, 627; see also, N. Wade: "Supreme Court to Say, if Life is Patentable", *Science, 206* (1979) 664; and, the report in the *Financial Times*, June 2, 1981, p. 13, "General Electric wins patent for oil eating bug".

[17] There are already initial experiments of this kind within universities and large research facilities. See A. L. Edinghaus: "Wirtschaftliche Verwertbarkeit—Künftig 'erste Forscherpflicht'?" ("Economic exploitability—In Future 'the Researcher's Foremost Obligation'?"), *Aktuelle Wissenschaft 1981*, No. 1, p. 2.

[18] Added to the continuing possibility of applying for national patents is the possibility, since June 1, 1978, of applying for a European patent under the European Patent Convention of 1973, as well as the possibility added to that, of applying for national as well as European patents by way of the Patent Cooperation Treaty (PCT) see *inter alia*, R. Singer, "Das neue europäische Patentsystem" ("The New European Patent System"), Nomus Verlag, Baden-Baden 1979, p. 159ff.

[19] But, he can also take advantage of the help of the Patentstelle für die Deutsche Forschung der Fraunhofer-Gesellschaft (Patent Bureau for German Research of the Fraunhofer-Gesellschaft) in Munich, which after examining the invention may finance and undertake the patent application. See, A. Hlawaczek, "Überblick über die Arbeit der Patentstelle für die Deutsche Forschung" ("Summary of the Work of the Patent Bureau for German Research"), *FhG-Berichte 4/79*, p. 83.

[20] For the employee-invention law, see, E. Reimer, H. Schade, H. Schippel, "Das Recht der Arbeitnehmererfindung" ("The Employee Invention Law"), 5th edit. Berlin 1975; H. Schippel: "Compensation of Employee Inventors in Germany", (1973) E. Schmidt.

[21] The situation has recently been examined more closely in a discussion involving politicians, scientists, industrialists and representatives of the Ministries in the Bavarian Parliament. Cf. the *Süddeutsche Zeitung*, February 24, 1981.

[22] See, *e.g.*, the Jahrbuch der Max-Planck-Gesellschaft, *1978*, 727; *1980*, p. 776; see also [8].

[23] Also, *Albert Einstein* applied for patents for a number of inventions. See, "Einsteins Patente", *neuerer B 1979*, 202.

[24] For existing patent information services, see, J. Straus: "Vorhandene Informationsmöglichkeiten in der Patentliteratur" ("Information Possibilities Actually Available from Patent Literature"), *GRUR 1981*, 217.

[25] The life of *Karl Ziegler* and his scientific and financial success is described by *G. O. Schenk*, "Karl Ziegler", Yearbook of the Royal Society, Edinburgh, 1975, p. 1.

[26] See a) F. K. Beier: "Scientific Research, Patent Protection and Innovation", *International Review of Industrial Property and Copyright Law (IIC) 1975*, 367; b) F. K. Beier, J. Straus: Der Schutz wissenschaftlicher Forschungsergebnisse. Verlag Chemie, Weinheim 1982, 20pp.

[27] Cf. [26b], Ch. IV (No. 45ff.).

[28] Cf. [26b], No. 83.

[29] See, O. Bossung: "Stand der Technik und eigene Vorverlautbarung im internationalen, europäischen und nationalen Patentrecht" ("State of the Art and One's Own Prior Disclosure in International, European and National Patent Laws"), *GRUR Int. 1978*, p. 381; E. von Pechmann: "Ist der Fortfall der Neuheitsschonfrist des §2 Satz 2 PatG noch zeitgemäß?" ("Is the Abolition of the Grace Period in §2 (2) of the Patent Act Still Opportune?"), *GRUR 1980*, 436; also [26b], No. 95.

[30] N. Wade notes (cf. [16]) that the patent application for the basic invention by *Boyer* in the field of genetic engineering, was only made after a Stanford University official responsible for patents had read about *Boyer*'s work in the New York Times. The application could still just be effected within the one-year grace period which exists in the USA.

Organometallic Aspects of the Fischer-Tropsch Synthesis

By Wolfgang A. Herrmann*

In memoriam Rowland Pettit

The Fischer-Tropsch Synthesis counts among the industrial-scale processes having a versatile and broad product range, and has for decades offered the most attractive possibility for the use of coal as a source of heating oil and fuels. This conceivably simple reaction, the catalytic hydrogenation of carbon monoxide, generally leads to simple hydrocarbons as well (*i.e.* short chain olefins) that have been sought as chemical feedstocks since the oil crisis of the seventies, but fails to provide the large-scale, economic process required, due in large part to the minimal selectivity of traditional Fischer-Tropsch processes. In an effort to solve this problem current research in this sector is concerned not only with the optimization of old and the development of new catalytic systems, but also increasingly with the elucidation of numerous relevant reaction mechanisms. This article will discuss, from the viewpoint of an organometallic chemist, the significance of typical model reactions, both with regard to some fundamental aspects of synthesis gas chemistry, and in comparison with previous views concerning the mechanism of the Fischer-Tropsch Synthesis. The importance of various unique classes of complexes that have been studied in the context of Fischer-Tropsch chemistry is also evaluated with regard to their importance in the synthesis of hydrocarbons from carbon monoxide and hydrogen. It emerges that the primary steps of the reductive oligomerization of carbon monoxide are best described by the carbide/methylene mechanism, as originally proposed by *Hans Fischer* and *Franz Tropsch*.

1. Introduction

The versatile and technically well-established Fischer-Tropsch Synthesis[1-3] has recently joined olefin metathesis[4] as one of the most attractive and productive areas of organometallic research. The mechanistic features of the Oxo-synthesis have long since been explained[5], and the elegant model studies of *Casey, Katz, Grubbs,* and *Schrock* into the mechanism of olefin metathesis have reached their culmination point. Nevertheless, the mechanistic steps of the catalytic hydrogenation of carbon monoxide continue to be strongly debated.

At first glance the Fischer-Tropsch synthesis obeys the trivial-looking, idealized equation (a)

$$n\,CO + 2n\,H_2 \rightarrow -(CH_2)_n- + n\,H_2O \qquad (a)$$
$$(\Delta H_{500\,K} = -39.4\ \text{kcal/mol})$$

giving in an exothermic reaction a plethora of products including straight chain alkanes, alkenes, alcohols, aldehydes, carboxylic acids, esters, as well as arenes. The highly selective Union Carbide process, a rhodium- and ruthenium-catalyzed ethylene glycol synthesis[6], as well as the predominantly nickel-catalyzed production of methane from synthesis gas ("CO methanation")[7], are notable special cases of CO hydrogenation. It is still not known, however, whether these processes involve uniform reaction sequences. The comprehensive mechanisms proposed for the catalytic formation of Fischer-Tropsch products are particularly speculative, since the classical, low-selectivity synthesis normally employs heterogeneous alkaline iron and cobalt melt- or precipitation catalysts, under which conditions a confusing array of parallel and subsequent reactions appears to occur. The spectrum of products is virtually always dominated by aliphatic and α-olefinic hydrocarbons, but is strongly affected by rather small changes in pressure and temperature, the catalyst and its preparation and promoter content, as well as some parameters of the process-technology. For example, *Pichler* has shown that the use of specific ruthenium catalysts at high pressure (up to 2000 bar) and relatively low temperature leads to high-melting, straight chain paraffins ("polymethylenes") largely identical with Ziegler polyethylene, and with an average molecular weight of up to 240000. By way of contrast, rhodium catalysts yield low molecular weight oxygenated products[2a,b]. In the Mobil process, the synthesis gas reaction induced by ZnO/Cr_2O_3 catalysts (high pressure) or copper-containing catalysts (medium pressure) is utilized for the synthesis of methanol, which, in turn, is subsequently converted into gasoline type hydrocarbons by means of zeolite supported catalysts. The activity and selectivity of the catalyst is particularly sensitive to the degree of alkalization, which is thought to increase the ability of the catalyst to chemisorb the reactants, as well as increase the rate of all carbon monoxide consuming reactions (CO reduction, water gas shift reaction, carbide formation, *etc.*). Finally the *water gas shift equilibrium*[3b]

$$CO + H_2O \rightleftarrows H_2 + CO_2$$
$$(\Delta H_{500\,K} = -9.5\ \text{kcal/mol})$$

affects not only the composition of the coal-derived synthesis gas (CO/H_2) but also the nature and molecular weight distribution of the Fischer-Tropsch products.

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2. Present-Day Objectives of the Fischer-Tropsch Synthesis

The necessity of developing economically profitable alternative sources of chemical raw materials as a result of the oil crisis of the seventies has completely reversed the selectivity goal of the Fischer-Tropsch synthesis. The efficiency of a catalyst was previously measured in terms of the "degree of liquefaction", resulting from the production of liquid fuels from synthesis gas, whereas nowadays the achievement of as narrow as possible a product distribution is of particular interest (for example, short chain olefins as chemical feedstocks, $C_5 \ldots C_{11}$ olefins for conversion into softener alcohols, $C_9 \ldots C_{10}$ aliphatics as detergent raw materials). Economic estimates lead to the conclusion that a complete replacement of petroleum products by hydrocarbons derived from synthesis gas is not possible, at least at present, in the Federal Republic of Germany. Although short-, medium length, and long-chain alkenes bring far higher returns as chemical feedstocks than as fuels and heating oils, this reversion would result in a 6—7-fold increase in the demand for hard coal (4 t per 1 t primary product, *i.e.* 600 million tons per year). Hence, the Fischer-Tropsch synthesis could compete with petroleum only if the process selectivity could be considerably improved, and if crude oil were to be scarce and coal comparatively cheap. The last two of these conditions are already met with in some countries, *e.g.*, South Africa and Australia. Therefore, allowing for a certain amount of flexibility in the demand for basic chemicals, a new generation Fischer-Tropsch synthesis must be marked by high selectivity in order to compete effectively. It is generally agreed, that the development of new types of catalysts deserves primary attention. In view of the advanced state of our technical knowledge of the classical Fischer-Tropsch synthesis the emphasis will be on the use of alkalized heterogeneous catalysts, but a great deal of effort will be directed towards the development of homogeneous catalysts[8] with their potential for selective product control. This goal seems to be within reach now that the metal-induced model reactions discussed in this article have not only characterized numerous previously unknown classes of compounds, but also decidedly increased our understanding of the elementary steps of carbon monoxide hydrogenation.

3. Limiting Conditions for Reaction Mechanisms

Every possible reaction mechanism for the Fischer-Tropsch synthesis must fulfil the following limiting conditions: 1) The reaction formally obeys polymerization kinetics giving a Schultz-Flory product molecular weight distribution. 2) α-Olefins and alcohols are primary products. ^{14}C-Tracer studies[1b,9] have established that saturated hydrocarbons arise independently by olefin hydrogenation subsequent to the actual chain growth process. Beyond that, there is no doubt α-olefins as well as alcohols and aldehydes are incorporated into growing chains. 3) The chain termination steps do not deactivate the catalytic center, for the rate of chain growth normally remains unchanged for weeks. 4) The formation of hydrocarbons from synthesis gas according to eq. (a) results in the reduction of carbon monoxide to CH_2 building blocks with concomitant formation of water (!).

4. The Carbide/Methylene Mechanism

In one of their first publications, *Fischer* and *Tropsch* considered CO hydrogenation as a "Polymerisation von Methylen-Gruppen" wherein surface carbide species were formulated as the pivotal precursors of the methylene groups[10a]. Since the discovery and complete characterization of stable transition metal-methylene complexes with terminal **1**[11,12] and with bridging CH_2-functions **2**[13,14] (Fig. 1), this viewpoint has been revived through results of elegant experiments. Thus, nickel, cobalt, and ruthenium-based catalysts were doped with labeled carbon using the Boudouard disproportionation of ^{13}CO and were then treated with $^{12}CO/H_2$ mixtures under Fischer-Tropsch (F-T) conditions. The resulting product mixture consists mainly of $^{13}CH_4$ and hydrocarbons containing *several* (!) ^{13}C-atoms in one and the same molecule[10b].

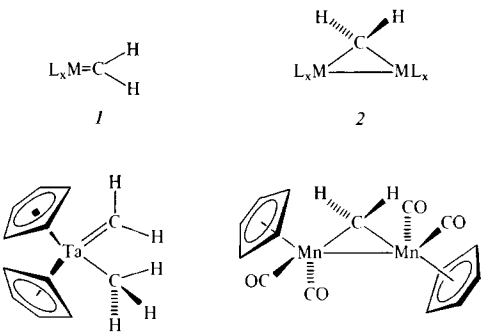
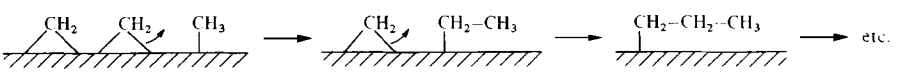


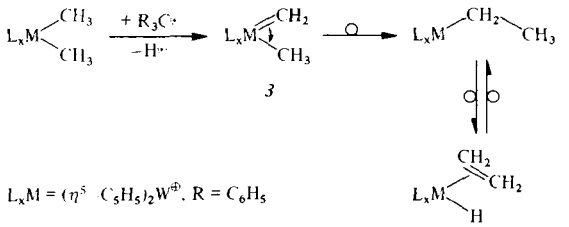
Fig. 1. Typical methylene complexes of type **1** with terminal ligands and of type **2** with bridge-bound ligands. The mononuclear tantalum complex is accessible by selective deprotonation of the cationic precursor $[(\eta^5\text{-}C_5H_5)_2Ta(CH_3)_2]^+$ [11, 12], while the methylene bridge of the dinuclear manganese complex is achievable with diazomethane [13, 14].

Other results support the conclusion that carbon monoxide rapidly dissociatively chemisorbs on F-T catalysts to give carbide species, which then react with hydrogen to give oxygen-free CH_x intermediates ($x = 1-3$) and in this way result in chain growth (Scheme 1)[10b]. Mention should be made in this context that surface-bound CH_2 groups can also become involved in competitive olefin metathesis[4,10b]. Furthermore, carbidization of the catalyst under



Scheme 1.

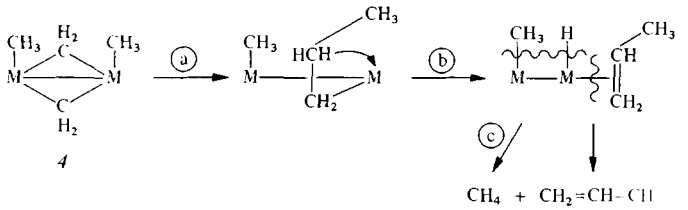
real F-T conditions is well known[1a]. The mechanistic viability of the insertion of a methylene group into a metal-methyl bond finally leading to polymerization as outlined in Scheme 1, could recently be verified in a stoichiometric model reaction of an electrophilic CH_2-complex **3** with the help of labeling studies[15a]. Beyond that, the products of



3

$L_xM = (\eta^5\text{-}C_5H_5)_2W^{\oplus}$, $R = C_6H_5$

the thermolysis of dinuclear μ-methylene-methyl complex **4** impressively confirm the methylene insertion step[15b]: At 350 °C the *cis*-isomer yields primarily methane (48%), ethylene (20%), ethane (2%), and propene (30%); only traces of propane and C_{4+} hydrocarbons are formed, while cyclopropane is not formed at all. Control experiments rule out the participation of π-bonded $C_5(CH_3)_5$ ligands in the synthesis of the observed hydrocarbons. Of particular importance is the predominance of propene over propane—α-olefins are among the primary products of the Fischer-



4

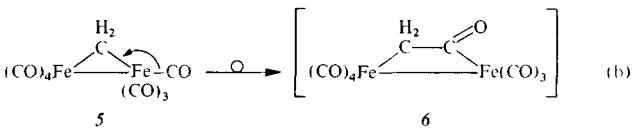
$M = (\eta^5\text{-}C_5Me_5)Rh$

Scheme 2. ⓐ—ⓒ, see text.

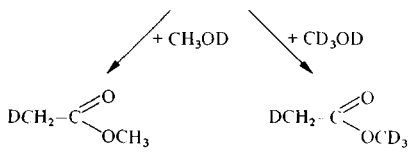
Tropsch synthesis! The most pertinent aspects of the thermal decomposition of the dinuclear system **4** are summarized in Scheme 2; they include the initial double CH_2-insertion ⓐ (C—C coupling), and the two conceivably most important termination steps under real Fischer-Tropsch conditions, *e.g.*, the kinetically highly favored β-hydrogen elimination ⓑ and the dinuclear alkyl/hydrogen reductive elimination ⓒ (giving alkanes; in this case, methane). The latter process liberates the olefin, in this case propene. Bis(μ-alkylidene) complexes *without* additional alkyl ligands generally decompose to give only olefins, resulting from carbene dimerization[15c]. The mode of coordination of CH_2-species attached to surfaces (**1** or **2**) remains uncertain, especially considering the fact that specific dinuclear metal complexes can contain both terminal as well as bridging methylene ligands[16]. Recent HMO calculations indicate that the C-atoms of the surface-bound bridging methylenes are not tetrahedrally coordinated, as in **2**, but are planar coordinated[23a], whereas in all isolable dinuclear complexes reported in the literature a distorted tetrahedral structure is found, irrespective of whether a metal-metal bond is present at the same time or not[14].

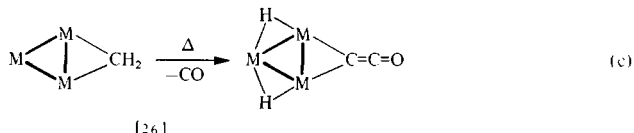
4.1. Dimetallacyclopropanes

Dimetallacyclopropanes **2** comprise a structurally and spectroscopically well established class of compounds and represent the most simple available model systems for the simulation of the chemistry of surface-bound methylene or alkylidene species. They are marked by an especially high tendency toward incorporation of olefins (→olefin homologation) and acetylene derivatives[14b], as well as a high reactivity *vis-à-vis* hydrogen (→methane)[14b] and protic acids (→μ-methylidyne complexes)[14b]. A μ,η^2-ketene intermediate **6** (CO-insertion) is proposed to account for the interesting formation of methyl acetate (80%) in the decomposition of the μ-methylene iron complex **5** with methanol according to eq. (b); nothing is known, however, about the fate of the complex fragment[17a]. This reaction may provide a starting point for a better understanding of catalytic *alcohol homologation* processes. Also worth mentioning in this respect is the observed carbonylation of a bridging methylene group to give the corresponding ketenylidene function [eq. (c)][17b]. Should recent reports of an as yet mechanistically poorly understood isomerization of an alkylidene chain along a metal-metal unit turn out to be a general pathway [eq. (d)][17c], then this process offers yet another model for the isomerization of mobile alkylidene species on metal surfaces[18]. The equilibrium (d) allows the bridging methylene with the lowest degree of substitution [$R(CH_2)_{x+1}CH$] to be achieved[17c]. Model studies have established that elimination of an alkylidene species from the metal centers is strongly favored by β-hydrogen migration (→olefins), but is much less favorable than decarbonylation if it should happen that the complex displays CO ligands at the same time[14b].



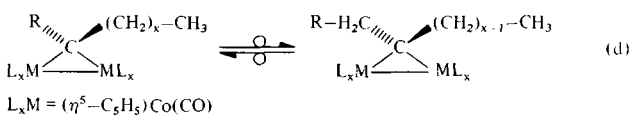
5 *6* (b)





(c)

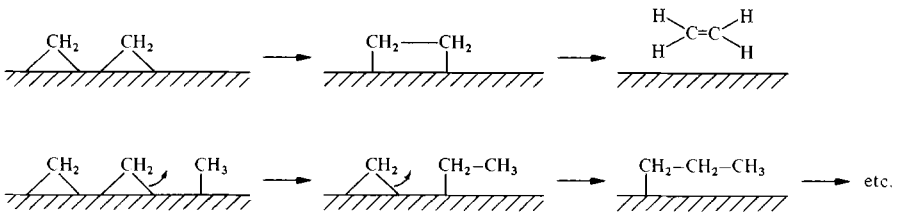
$M_3 = Os_3(CO)_{11}$ [26] $M_3 = Os_3(CO)_9$



(d)

$L_xM = (\eta^5\text{-}C_5H_5)Co(CO)$

The most convincing support of the carbide/methylene mechanism was provided by a detailed investigation, *inter alia*, of the Fischer-Tropsch catalyst-induced decomposi-



Scheme 3.

tion of gaseous diazomethane[10c]. *Exclusively* ethylene and dinitrogen are formed on Ni-, Pd-, Fe-, Co-, Ru-, and Cu-surfaces in the temperature range 25–250 °C at atmospheric pressure. Therefore, in the absence of other reactants, only dimerization and no polymerization of the surface absorbed CH_2-fragments occurs (Scheme 3, top). On the other hand, reaction of a mixture of H_2/CH_2N_2 over Co-, Fe-, and Ru-catalysts leads to a wide variety of hydrocarbons (primarily linear alkanes and olefins) with the isomer and molecular weight distribution of typical Fischer-Tropsch reactions! The results for H_2/CH_2N_2 and H_2/CO reactions under comparable conditions, illustrated in Figure 2, suggest the same polymerization mechanism as in Scheme 3 (bottom). Besides CO-activation (→carbide→methylene) the dissociative chemisorption of H_2 is also a prerequisite for this mechanism: If the catalyst surface (*e.g.* copper) is not capable of this latter process then no Fischer-Tropsch reactivity is observed, and, as expected, CH_2N_2 decomposition gives only ethylene, even in the presence of H_2[10c]. The production of CH_4[19a] in the reaction of H_2 (*ca.* 12 bar, benzene, 60 °C) with the isolable model complex $(\mu\text{-}CH_2)Fe_2(CO)_8$ does not contradict this mechanism, since multiple CH_2-insertions are not possible in this *mono*methylene system. Furthermore, the selective formation of ethylene in the reduction of coordinated carbon monoxide with AlH_3[19b] is probably attributable to the methylene complex as formulated in eq. (e): Thus, $Cr(CO)_6$ gives exclusively ethylene, in a rapid reaction (15 min, 22 °C), even with a large excess of AlH_3; only after acidification of the reaction mixture with H_2SO_4 are methane and ethane formed.

Finally, in accord with the chain growth formalism of Scheme 3 (bottom) it is found that the composition of the product gases of the F-T synthesis over different catalysts is identical with that of the hydrocarbon mixture obtained upon treatment of the expended catalyst with acid[19c].

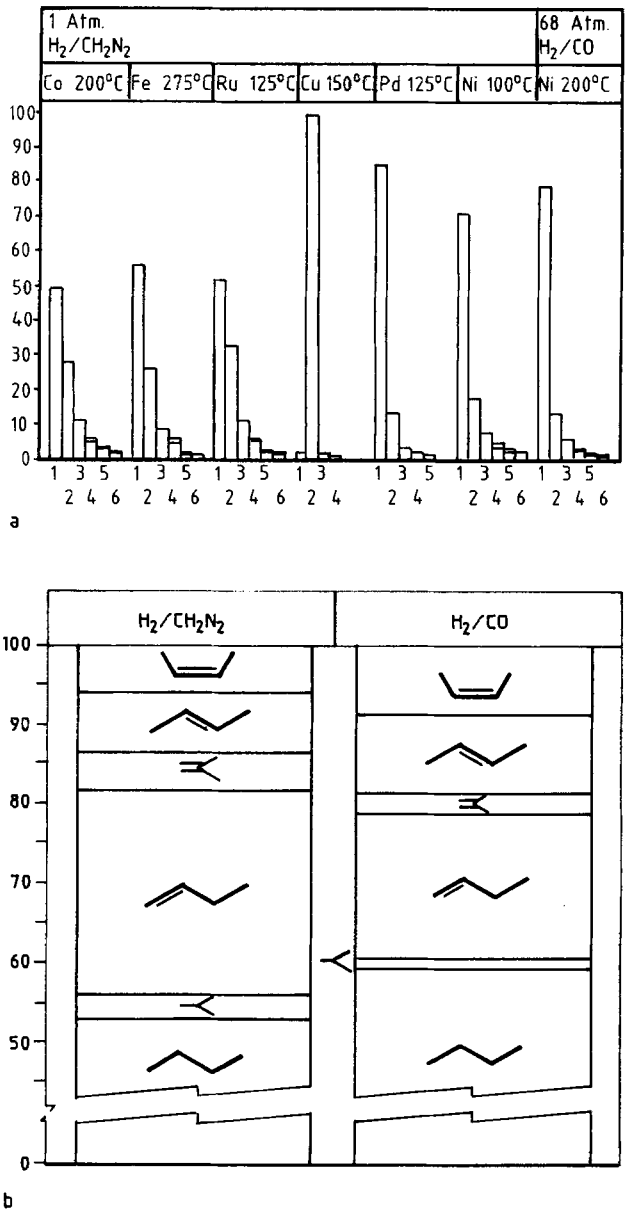
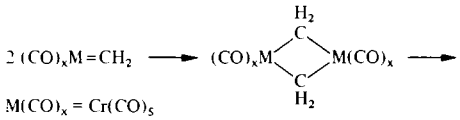
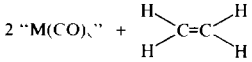


Fig. 2. a) Molecular weight distribution of hydrocarbon fractions formed from H_2/CH_2N_2 and H_2/CO on F-T catalysts. Alkanes and olefins are presented together corresponding to their chain lengths (abscissa). The block starting from the zero line represents the proportion of linear hydrocarbons, while the proportion of branched isomers are represented by the upper sections. Ordinate: Wt.-%. b) Comparison of the C_4-hydrocarbon fractions obtained from H_2/CH_2N_2 and H_2/CO, resp. (39% cobalt/silica catalyst, 210 °C, 1 bar). Ordinate: Wt.-%. (After [10c].)

4.2. Carbide Clusters

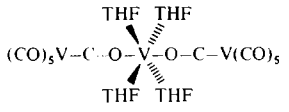
The metal-induced decomposition of carbon monoxide leading to formation of cluster complexes with "naked" C-



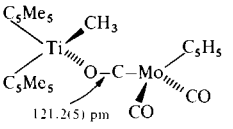


atoms as ligands is no longer a curiosity in organometallic chemistry. The rupture of the C—O bond, especially on metal surfaces, may be facilitated by the coordination of

both atoms[20], as has been demonstrated in a series of structurally well-characterized multinuclear complexes (*e.g.* **7** and **8**; THF = tetrahydrofuran)[21]. The η^2,μ_3-complexation in the niobium cluster **8d** leads to an extreme lengthening of the C—O distance (*ca.* 130 pm)[21e]. The ytterbium(III) complex **8e** is an illustrative example, revealing the oxophilic character of lanthanoid elements. Here too, the C—O bond of the carbonyl bridge is significantly weakened as compared with the usual type of complexation[21f].

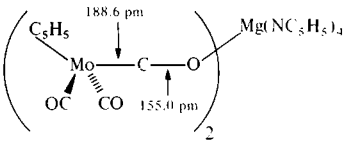


7[21a]



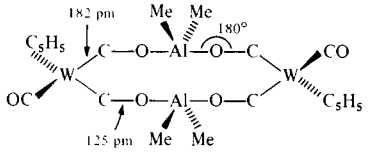
νCO = 1623 cm^{-1} (Nujol)

8a[21b]

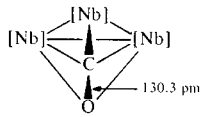


νCO = 1667 cm^{-1} (Nujol)

8b[21d]



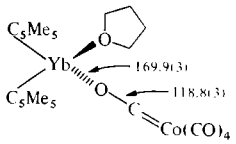
8c[21c]



νCO = 1330 cm^{-1} (KBr)

[Nb] = $(\eta^5$-$C_5H_5)$Nb(CO)$_2$

8d[21c]



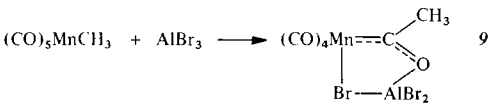
νCO = 1798, 1761 cm^{-1}

∢ Yb, O, C = 163.0(2)°

∢ Co, C, O = 177.8(2)°

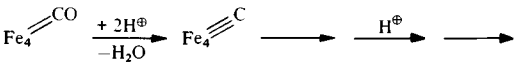
8e[21f]

Besides *O*-complexation, the activating effect of Lewis acids has also been well investigated since the time that *Shriver et al.* carried out their formative studies in this sector[22a,b]. Thus, the addition of aluminum tribromide increases the rate of the intramolecular methyl migration by orders of magnitude. In the resulting X-ray structurally



9

characterized product **9** the "ambiphilic" Lewis acid stabilizes not only the free coordination site on the transition metal formed as a result of methyl migration, but also complexes the basic acetyl function through the electron-deficient aluminum atom. Alumina surfaces show a comparable effect on the rate of methyl-to-carbonyl transfer to that observed for $AlBr_3$ in solution[28].

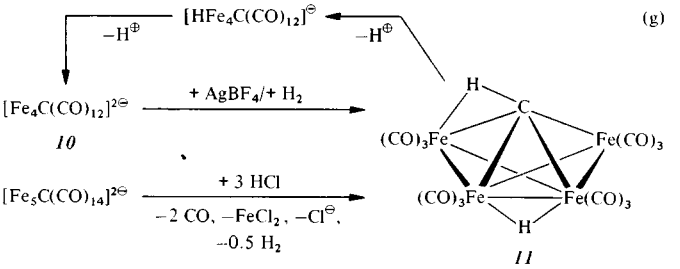


(f)

$CH_4 + Fe^{2\oplus} + CO$–Fe–Compounds

Treatment with Brønsted acids allowed an anionic carbonyl complex to be smoothly decomposed with formation of CH_4 and H_2 [eq. (f)]. It was proven by deuterium labeling experiments, that the hydrocarbon hydrogens came from the added acid[22c]. Accordingly, the mononuclear and dinuclear complexes $(\eta^5$-$C_5H_5)$Fe(CO)$_2$Li and Mg[$(\eta^5$-$C_5H_5)$Fe(CO)$_2$]$_2\cdot x$THF produce methane, ethylene, and ethane as a result of η^2, $\mu(C,O)$-coordination, even at low temperatures. The formation of cationic Fe=CH_2 species in this reaction has been postulated[22d]. The plausibility of these proposed mechanisms, however, is diminished by the normally low yields of hydrocarbons produced in the course of such reactions. In the light of this, strongly oxophilic centers should favor carbide formation. However, it is exactly such transition metals, from groups IV and V, which strangely enough hinder Fischer-Tropsch reactivity.

Muetterties has recently developed rational synthetic methods for the generation of carbide complexes[23], and, moreover, has shown[24a] that structurally characterized compounds with four-fold coordinated anionic carbide C-atoms react with H_2 under oxidative conditions to give CH-functionalities [eq. (g)], and are thus to be seriously considered as key species in the formation of CH_2-moieties from CO. Alternatively, it proved possible to form C—H bonds by protonation [eq. (f) and (g)]. Rapid hydrogen exchange between the C*H* and the Fe—*H* groups would indicate the importance of such processes on metal surfaces. The fully-characterized μ_4,η^2-CH-three-center bond[24a,b] in



(g)

the "butterfly" molecule **11** (see Fig. 3) appears to approach the energetically most favorable form of methylidyne complexation on top of specific metal surfaces[24c], and emphasizes the importance of M—H interactions in

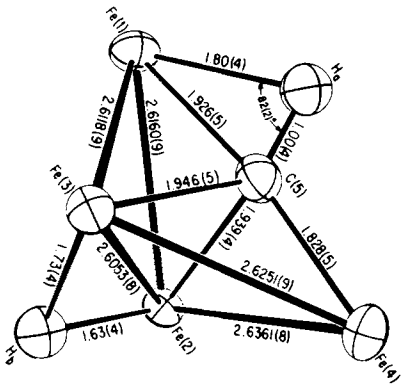
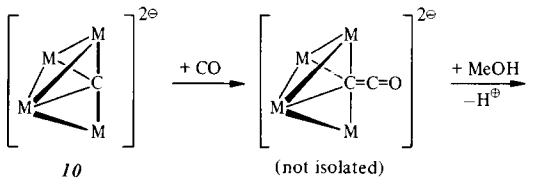
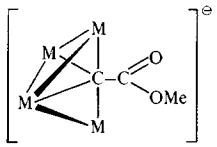


Fig. 3. Structural section from the μ_4,η^2-methylidyne cluster **11**. For sake of clarity the carbonyl ligands have been omitted; bond lengths in pm (after [24b]; reproduced by permission of the American Chemical Society).

catalytic processes. Besides oxidative addition of H_2, carbide clusters (such as **10**) are also capable of carbonylation[24d].



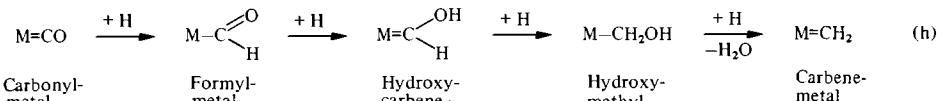
10 (not isolated)



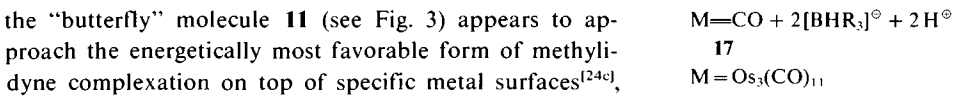
M = $Fe(CO)_3$

4.3. Stepwise CO-Hydrogenation

A much discussed alternative approach to methylene species is the *stepwise* hydrogenation of (in **12** metal-coordinated) carbon monoxide, a reaction sequence [(h)] which should involve the structural types **13**—**15**[12,14,25], that are now preparatively available as more or less stable mono- and



dinuclear complexes. Starting from the trinuclear osmium complex **17**, and using spectroscopy and [^{2}H]-labeling experiments, the entire sequence **12**—**16** has been established by consecutive reaction with H^- and H^+ as shown in the following equation[26]:



Of particular significance here is the observation, that the *hydride* hydrogen from the reductant K[BH(O—*i*-$C_3H_7)_3$] appears in the methylene group of **18**, whereas the subsequently added phosphoric acid (H^+) is required for the detachment of the carbonyl oxygen. Consistent with this finding, formation of the methylene cluster **18** does not occur when these reagents are added to the carbonyl complex **17** in the opposite order. The intermediate anionic formyl complex $Os_3(CO)_{11}[C(=O)H]^-$ produced by H^--addition is characterized by a ^{1}H-NMR signal observed at $\delta = 16.0$ as well as by an intense νCO band at 1577 cm^{-1} [26].

4.4. Formyl Complexes

Since the extensive studies of *Casey*[25a] and *Gladysz*[25b], structurally well-characterized mono- and multinuclear complexes with up to two η^1-bound formyl functionalities per metal are readily accessible in large quantities by reduction of the appropriate cationic or neutral metal carbonyl precursor with commercially available hydride reagents. Formyl ligands can easily be detected ^{1}H-NMR spectroscopically by means of low field signals in the region $\delta > 10$ ppm. Complex *anions* of this kind are chemically characterized by a pronounced hydride reactivity: Thus the extensively investigated iron complex $[L(CO)_3Fe\{C(=O)H\}]^-$ ($L = P(OC_6H_5)_3$) is suitable not only for the smooth reduction of 2-butanone to 2-butanol (92%), but also for hydride transfer to neutral Fischer carbenes or carbonylmetal compounds, for example $(CO)_5W{=}C(OCH_3)C_6H_5$ or $Re_2(CO)_{10}$[25a]. Moreover, reactivity studies suggest participation of the oxo-carbene structure $M{=}C(O^-)H$ in the ground state of anionic formylmetal systems. In the absence of appropriate reactants the irreversible decarbonylation typical of neutral formyl complexes normally dominates, whereby generally good yields of metal hydride derivatives result according to the scheme M—C(=O)H → M—H + CO[25a,b]. Occasionally, metalformyls also undergo intermolecular Claisen-Tischtschenko-type dismutation reactions. Thus, the neutral formylmanganese complex of composition *mer*-$(CO)_3[P(OCH_3)_3]_2Mn[C(=O)H]$ decomposes above 0° C with CO_2- and CO-elimination and concomitant formation of both the known mononuclear methyl derivative *mer*-$(CO)_3[P(OCH_3)_3]_2MnCH_3$ (40%) and the novel dinuclear complex $Mn_2(CO)_6[P(OCH_3)_3]_4$ (8%). This observation nicely points to a general, metal-centered pathway starting from formyl and leading to methyl functionalities[25d].

4.5. The Formyl/Hydrido(carbonyl) Equilibrium

The formation of the first C—H bond is of crucial importance to the stepwise, that is non-dissociative, CO reduction. Although the formyl/hydrido(carbonyl) equilibrium (i) has been cited for years as an analogous case to the well-established, completely reversible acetyl/methyl(carbonyl) system[35] in the explanation of kinetic data for CO substitution in carbonyl(hydrido)metal compounds, recent observations have strengthened the suspicion that the isomerization **19**→**13** does not occur to any appreciable extent for thermodynamic reasons. From model reactions [eq. (j)], carried out with isolable formyl and acetyl complexes, an equilibrium ratio of $K_1/K_2 > 10^5$ was ascertained, from which it follows that the kinetically moderately stable formyl species are thermodynamically less stable by a few orders of magnitude than the analogous acetyl complexes[25a]. Consequently, whereas decarbonylation (see *e.g.* Section 4.4) as well as the formyl→hydrido(carbonyl) reaction **13**→**19** can practically always be achieved preparatively, the reverse "CO-insertion" (**19**→**13**), as formulated in eq. (i), has not yet been observed. It can be supposed that the 20—30 kcal/mol greater stability of the M—H bond compared with a M—CH_3 bond is responsible for the strongly divergent equilibrium relationship in eq. (j).

19 $\quad H-M-CO \rightleftharpoons M-C(H)=O \quad$ *13* (i)

$(R_3P)(CO)(OC)(CO)Fe^{\ominus}-C(H)=O \rightleftharpoons R_3P + (CO)_4Fe^{\ominus}-H \quad (K_1)$

(j)

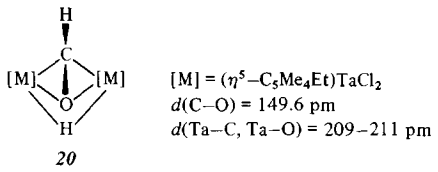
$(R_3P)(CO)(OC)(CO)Fe^{\ominus}-C(CH_3)=O \rightleftharpoons R_3P + (CO)_4Fe^{\ominus}-CH_3 \quad (K_2)$

$R = OC_2H_5$

$$K_1 = \frac{[R_3P]\,[(CO)_4Fe^{\ominus}-H]}{[(R_3P)(CO)_3Fe^{\ominus}-C(=O)H]}\,;\quad K_2 = \frac{[R_3P]\,[(CO)_4Fe^{\ominus}-CH_3]}{[(R_3P)(CO)_3Fe^{\ominus}-C(=O)CH_3]}$$

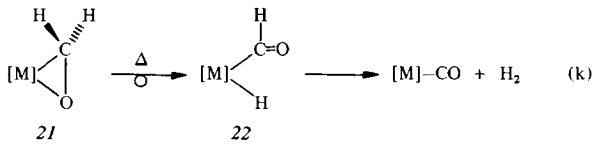
Nevertheless, it cannot be ruled out that formyl formation [eq. (i)] is favored on *heterogeneous* catalysts by an additional coordination of the formyl oxygen atom [cf. **20**—**22**, eq. (k)][27a,b], because Lewis acid effects of this kind also accelerate the formally analogous methyl group migration (CH_3—M—CO → M—C(=O)CH_3) by several orders of magnitude in homogeneous as well as heterogeneous systems (see Section 4.2).

Thus, the X-ray structurally characterized μ,η^2-formyl complex **20** originates from addition of CO to the hydrido-precursor $[(\eta^5\text{-}C_5Me_4Et)TaCl_2]_2H_2$[27a]; the equilibrium (l) has been demonstrated IR- and NMR-spectroscopically[27c]. Moreover, destabilization of M—CO bonds by d^0-metals should contribute to the preference for **13** [eq. (i)].



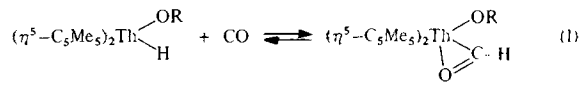
20

$[M] = (\eta^5\text{-}C_5Me_4Et)TaCl_2$
$d(C-O) = 149.6$ pm
$d(Ta-C, Ta-O) = 209-211$ pm



21 (stable up to 75°C)[27b] *22* (unstable)

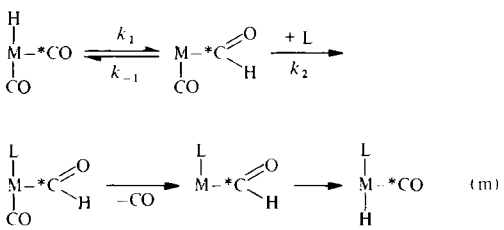
[M] = $Os(CO)_2[P(C_6H_5)_3]_2$



(l)

R = 1-*tert*-butyl-2,2-dimethylpropyl or 2,6-di-*tert*-butylphenyl

Several authors have recently commented[27d] on the well-known, abnormally fast CO-substitution in anionic, neutral as well as cationic carbonyl(hydrido)metal complexes (*e.g.* $HMn(CO)_5$), and have suggested that precisely the kinetic character of such reactions is attributable to only *small* concentrations of formylmetal intermediates [eq. (m)]. Earlier observations of *Basolo*, *Heck*, and *Brown*, concerning the reactivity of $H_2Fe(CO)_4$, $H_2Ru(CO)_4$ and their derivatives, would suggest that the thermodynamic



(m)

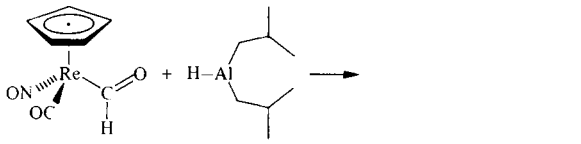
L = phosphane or phosphite, M = *e.g.* $Mn(CO)_3$ or $HFe(CO)_2$

instability of the formyl intermediate is a necessary prerequisite for the irreversible reaction of type **13**→**19** subsequent to substitution[27d]. The question as to the realizability of the equilibrium (i) on catalyst surfaces remains unanswered.

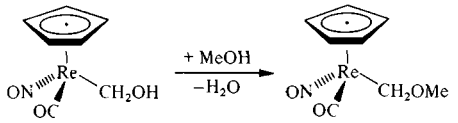
4.6. Hydroxymethyl, Methoxymethyl, Methoxy and Hydroxycarbene Complexes

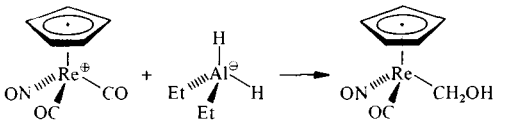
In principle, starting from formyl complexes, further reduction can lead to hydroxymethyl derivatives. Thus *Casey*

et al. described the clean reaction (n), achieved on using the potent hydride transfer reagent diisobutylaluminum hydride ("DIBAL-H"). It is to be noted, however, that hydroxymethyl ligands are often preparatively more easily accessible [eq. (o)] *via* direct reaction of the corresponding carbonyl compound with hydride derivatives of boron and aluminum (*i.e.*, BH_3, $[H_2AlEt_2]^-$, *etc.*)[25a,b]. The most striking property of hydroxymethyl complexes is their behavior towards methanol, with which they react to give methoxymethyl derivatives [eq. (n)][25a].



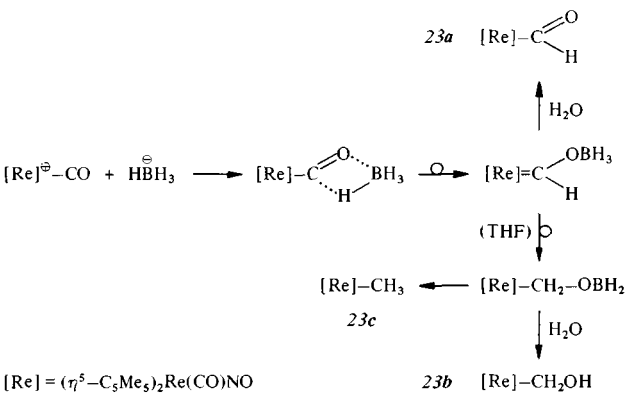
(n)



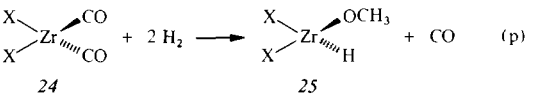


(o)

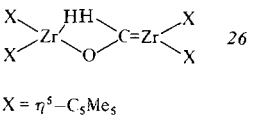
As model example for the stepwise reduction of coordinated carbon monoxide to isolable formyl, hydroxymethyl, and methyl ligands **23a—c**, *Sweet* and *Graham* have underscored the mechanism of the reaction of the complex cation $[(\eta^5\text{-}C_5Me_5)_2Re(CO)_2NO]^+$ with $NaBH_4$ in THF/H_2O[29a]. Under similar conditions, but dependent upon the water content of the solvent, the reaction time and temperature, the analogues of **23a—c** had already been prepared in surprisingly high yields (up to 95%) from the corresponding cyclopentadienyl complex[29b].



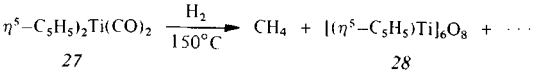
The first stoichiometric hydrogenation of complexed carbon monoxide in the homogeneous phase [eq. (p)] was achieved by altering the coordination atom in the ligand[30a,b]. This reaction is not entirely resolved mechanistically; however, it does provide a convincing example of the pronounced oxophilicity of electron-deficient transition metals [here: Zr^{II}] and for the strongly *hydridic* character ($M^{\delta+}$—$H^{\delta-}$) of their hydrido derivatives [here: $(\eta^5\text{-}C_5Me_5)_2ZrH_2$ or $(\eta^5\text{-}C_5Me_5)_2Zr(CO)H_2$]. If the conversion



(p)



24→25 really proceeds intermolecularly, then formation of zirconoxycarbene intermediates **26** is likely, as have been isolated from the reaction of $(\eta^5\text{-}C_5Me_5)_2ZrH_2$ with $W(CO)_6$[30a]. Reduction of the carbonyltitanium compound **27** with H_2 gives *methane* with concomitant formation of the structurally characterized hexanuclear oxo complex **28**[30b,c].



On using nucleophilic, H_2O-resistant hydridoniobium complexes [*e.g.*, $(\eta^5\text{-}C_5H_5)_2NbH_3$] for the reduction of electrophilic carbonylmetal compounds $M(CO)_x$, *Labinger et al.*[31a,b] observed selective alkane formation in specific cases [*e.g.* $Cr(CO)_6$, 2 h, 45 °C]; labeling experiments indicated that ethylene is the initial product, which is subsequently catalytically hydrogenated to ethane[31a]. The spec-

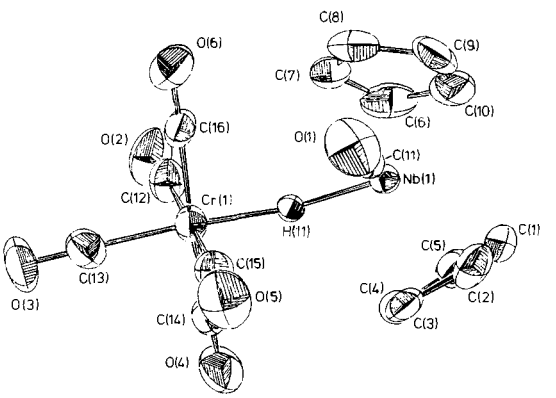
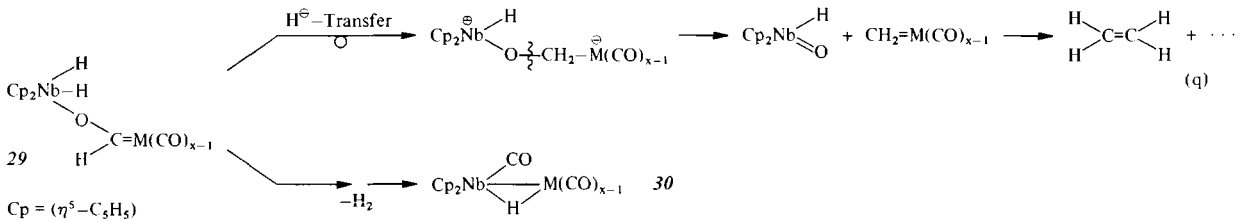


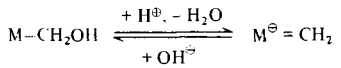
Fig. 4. Molecular structure of the μ-hydrido complex $(\eta^5\text{-}C_5H_5)_2Nb(CO)$—H—$Cr(CO)_5$ (type **30**), which is accessible as stable product by photolysis of $(\eta^5\text{-}C_5H_5)_2NbH_3$ and $Cr(CO)_6$. The formation of such compounds can be explained in terms of an oxycarbene intermediate (type **29**) through hydrogen transfer. Selected molecular data: Nb(1)—Cr(1) 345.3(2), Cr(1)—H(11) 118.2(102), Nb(1)—H(11) 182.4(99) pm; Cr(1), H(11), Nb(1) 137.4(54)°; $R_{iso}=0.045$, $R_{aniso}=0.077$. *(W. A. Hermann, M. L. Ziegler et al.*, unpublished results 1980/81).

troscopically identified initial dinuclear products of type **29**, however, open the possibility for side reactions [eq. (q)], which often lead to stable μ-hydrido complexes **30**

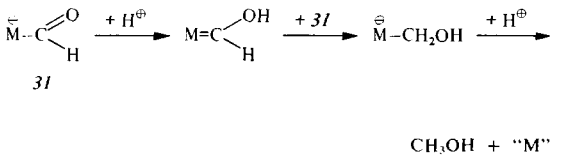


(Fig. 4)[31b–d]. Naturally, CO-reductions with hydridotransition metal complexes have proven to be much more complex than those with hydrides of the main group elements of comparable reducing strength (*e.g.*, Red-Al®, K-Selectride, *etc.*). Nevertheless, owing to their extreme tendency to hydrolyze, the latter are only suitable for stoichiometric reactions.

Methylene complexes $M^+{=}CH_2$ are related to their hydroxymethyl precursors by the acid/base equilibrium

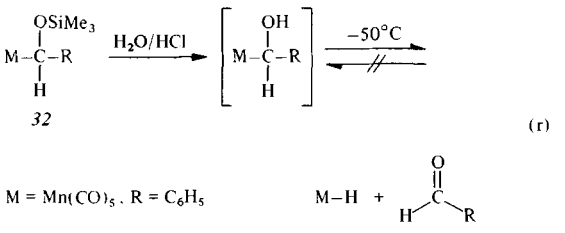


The protonation of anionic formyl derivatives such as **31** possibly involves hydroxycarbene complexes according to the overall sequence



M = Fe(CO)$_3$[P(OC$_6$H$_5$)$_3$]

Nevertheless, the primary formation of formaldehyde and its subsequent reduction by the hydride donor **31** cannot be ruled out[32]. Although the occurrence of free formaldehyde under real Fischer-Tropsch conditions is often not explicitly taken into consideration[2a], there is mass spectroscopic evidence for its presence among the initial products[33a]. According to a recent report concerning the protodesilylation of **32**, α-hydroxyalkyl complexes can be expected to irreversibly decompose to free aldehyde and the corresponding metal hydride [eq. (r)][34].

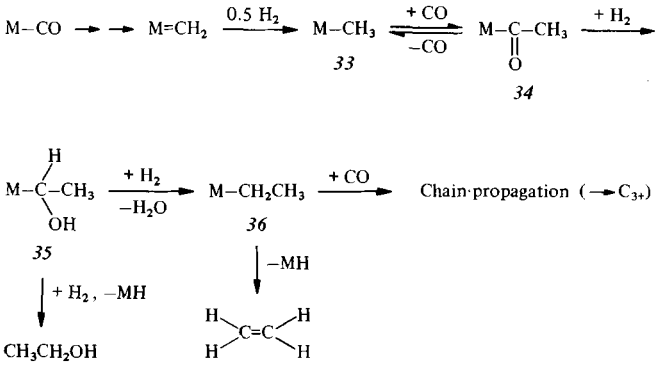


M = Mn(CO)$_5$, R = C$_6$H$_5$

It was very recently reported that free formaldehyde is capable of acting as a hydride donor toward ketones or higher aldehydes in the sense of metal-catalyzed Cannizzaro reactions with formation of the corresponding alcohols[33b]. Zirconocene dichloride-catalyzed reductive CO-oligomerization with diisobutylaluminum hydride gives a mixture of methanol, ethanol, 1-propanol, and 1-butanol (1.0 : 0.10 : 0.15 : 0.03)[33c]. Even octacarbonyldicobalt behaves as a weak catalyst for methanol formation from synthesis gas, but in this case rather drastic reaction conditions (300 bar, 200 °C) are required to achieve acceptable yields[33d].

5. The Carbon Monoxide Insertion Mechanism

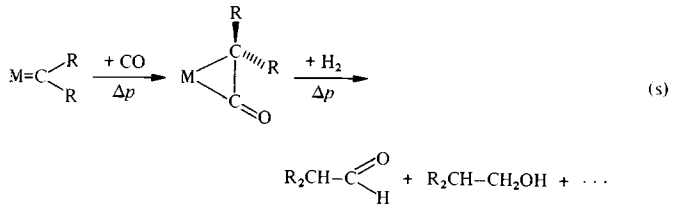
The most popular mechanism, but which according to the current state of our knowledge is presumably at best dominant in the synthesis of oxygen-containing F-T products, is based upon "CO-insertion"[35] into a metal-carbon bond as the fundamental chain growth step (alkyl migration)[2a]. According to this mechanism, the first M—CH_3 group **33** is formed by reduction of a metal-bound formyl intermediate, as outlined in principle in eq. (h). Subsequent reduction of the resulting acetyl moiety to an ethyl moiety is viewed as the key reaction along the path to consecutive incorporation of CO. If decarbonylation **34**→**33** is faster than alkyl transfer, then the formation of higher products will not result. A most important aspect of this



sequence is the reduction of α-hydroxyalkyl intermediates (*e.g.*, **35**) with cleavage of the metal-to-carbon bond to give alcohols, as well as β-hydrogen abstraction in the alkyl state (*e.g.*, **36**) to give α-olefins in competition with chain growth. On the other hand, alcohol formation could also arise from metal carbene species: mononuclear model systems for both hydrogenolytic cleavage of the carbene intermediate[36] and CO-addition have hitherto been established [eqs. (s)—(u)][37a,b,f].

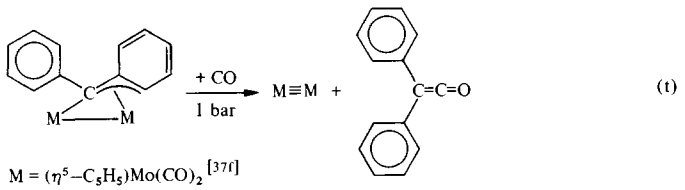
The latter reaction gives primarily the corresponding, in some cases isolable, structurally well-characterized ketene complexes (cf. Fig. 5)[14a,37a]. Decisive for the course of the reaction (u), is the metallocyclobutane/metal-olefin-me-

thylene equilibrium, that is also established for metallacycles of platinum[37b]. The observation of intramolecular CO-exchange in multiply metal-bonded ketenes suggests



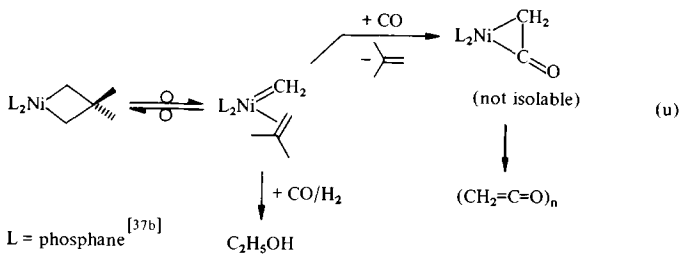
(s)

M = $(\eta^5-C_5H_5)Mn(CO)_2$, R = C_6H_5 [37a]



(t)

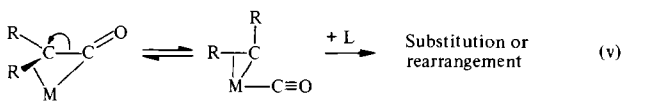
M = $(\eta^5-C_5H_5)Mo(CO)_2$ [37f]



(u)

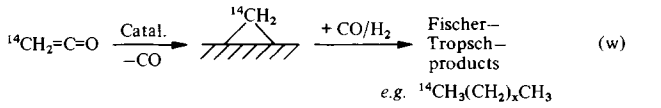
L = phosphane [37b]

reversible cleavage of a ketene C—C bond within the coordination sphere of the metal as in eq. (v) (Fig. 6)[37c]. Thus surface-bound ketenes could also take part in chain growth. In this connection, it should be remembered that incorporation of the methylene fragment from ketene into F-T products has been known for some time [eq. (w)][5a].



(v)

M = $Fe(CO)_3$, R = C_6H_5



(w)

Alternatively, it is possible to form ketene functionalities by carbene transfer to carbonyl-metal compounds[37e]. The synthetic step **34**→**36** has been established in the reduction of mononuclear acetyliron and acetylruthenium complexes with borane, and thus, in principle, could take place in catalytic cycles as well[37d]. The possibility of *selective* formation of oxygen-containing products by CO insertion

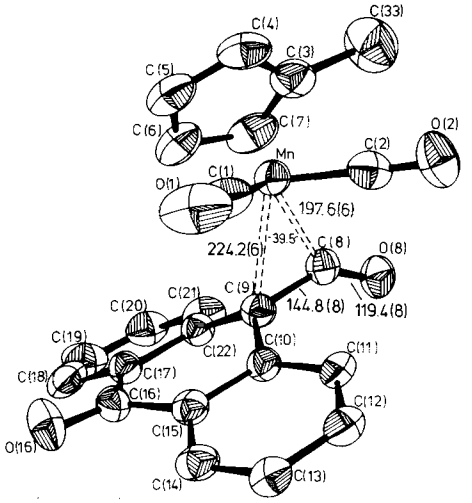


Fig. 5. Molecular structure of the ketene derivative dicarbonyl (η^2-10-carbonyl-9-anthrone)(η^5-methylcyclopentadienyl)manganese obtained by metal-induced carbene transfer to a manganese-CO function (bond lengths in pm, angles in degrees) [37e].

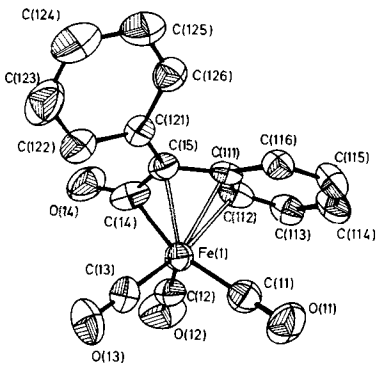


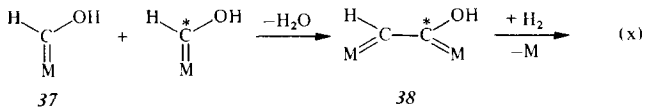
Fig. 6. Molecular structure of the η^1-η^3-diphenylketene complex $[(C_6H_5)_2C—C—O]Fe(CO)_3$. The intramolecular rupture of the C(14)—C(15) bond activated by complexation of the heterocumulene was established by labeling and crossover experiments [37c].

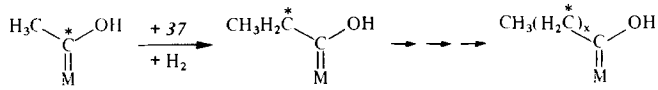
into surface-bound bridging alkylidenes was mentioned earlier (Section 4.1).

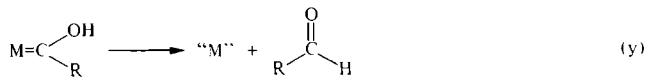
6. The Hydroxycarbene Mechanism

A proposal originally put forward by *Storch et al.*[1c,38] and later reiterated by *Kölbel et al.*[39] attributes chain growth to intermolecular ("multi-site") condensation reactions of hydroxycarbene species (*ex* formyl). Unfortunately, from the organometallic chemistry viewpoint, too little is known about the reactivity of the generally very unstable hydroxycarbene complexes, so it cannot be ascertained whether the proposed chain growth sequence [eq. (x)] should be considered seriously. A strong argument in favor of the formation of "enolic" primary complexes has been cited, *inter alia*, on the basis of investigations into the incorporation of alcohols and aldehydes into F-T products[1a]. But, at least in the case of homogeneous model systems, the selective hydrogenation of only *one* M=C bond in the dicarbene bridge **38** should be looked upon with scepticism. Moreover, the well-documented decomposition of isolable hydroxycarbene complexes *via* 1,2-hydrogen

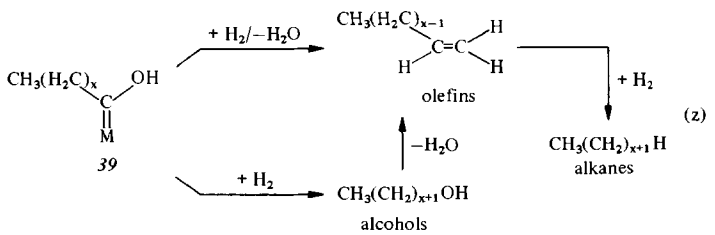
shift with concomitant formation of free aldehyde [eq. (y)] is also to be expected for surface-bound hydroxycarbenes[25c,40]. It is not certain whether this reaction, in the sense of a $d^n \rightarrow d^{n-2} \rightarrow d^n$ process, involves a hydrido(acyl) intermediate (d^{n-2}).







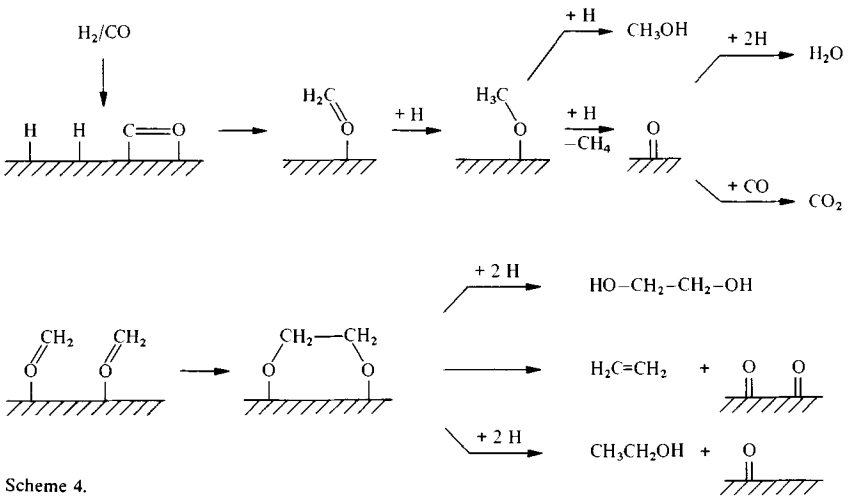
Model reactions for the reverse of eq. (y) are as yet unknown; this is unfortunate since their feasibility would not only give strong support to the mechanistic involvement of aldehydes in the Fischer-Tropsch synthesis but also would furnish an elegant synthetic route to hydroxycarbene complexes of which only scattered examples have so far been reported. Both these aspects represent a true challenge to the organometallic chemist.



A crucial test for the usefulness of the hydroxycarbene or hydroxymethylene model [eq. (x)] are the terminating steps outlined in eq. (z): None of the most conceivable degradation reactions considered here have been verified starting from isolable hydroxycarbene complexes of type **39**. It must be conceded, however, that the failure of these reactions to occur may possibly be due to coordinative saturation of the available substrates. Polynuclear systems bridged by hydroxyalkylidene functionalities and bearing supporting ligands that are prone to easy elimination could in fact basically change this pattern.

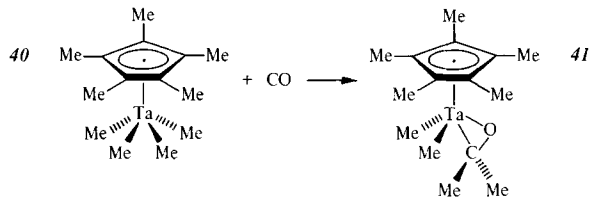
7. The Oxide Mechanism

The most recent mechanism put forward for the Fischer-Tropsch process, namely the "Oxide Mechanism" proposed by *R. S. Sapienza*[42] (Brookhaven National Laboratory) at an ACS meeting in August 1981, suffers from the grave disadvantage that it is quite speculative and, as yet, there is no suitable model system warranting its support. The general concept of this mechanism is that chain growth is accomplished on metal oxide surfaces and that the carbon atoms to be connected with each other do not touch the metal centers of the catalyst. In this context, formaldehyde is believed to be formed as the initial product and is anchored to the catalyst surface by means of the oxygen atom only. According to this view, the stability of the metal-to-oxygen linkage decidedly governs the product pattern (Scheme 4): After reductive coupling of the formaldehyde groups, hydrocarbons (in the case of strong M—O bonds) or oxygenates (in the case of weak M—O bonds) are formed. There is little doubt that the formation of oxidic surface layers has an effective influence upon the product pattern, but to overlook any possible metal-centered reaction steps would seem far too much of an oversimplification. Both the "Oxide Mechanism" as well as a related mechanism emphasizing the importance of hydroxy groups anchored to the catalyst surface[43] are inconsistent with the basic observation that even pronounced oxophilic metals (Ta^I) and metals in higher oxidation states (W^{IV}) do not bind simple *O,C*-ligands exclusively *via* the oxygen atom, and, conversely, that oxo(methylene)

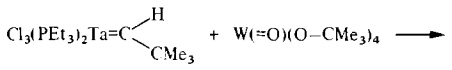


Scheme 4.

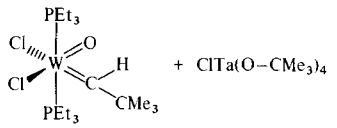
complexes obviously do not display any tendency to rearrange to aldehyde or keto derivatives. A typical example in support of this assessment is the well-characterized η^2-acetone complex **41,** which is formed by means of CO-insertion into the metal-methyl bond of the precursor molecule **40**[44]. In addition, the *Floriani* group has shown that *C*-coordination survives in the course of cycloaddition reactions between diphenylketene and certain titanium complexes[45]. Finally, the neopentylidene group of **42** is not transferred from tantalum to the oxo ligand of the carbene acceptor molecule **43,** but rather to its metal center. The



40 + CO → *41*



42 + W(=O)(O–CMe$_3$)$_4$ → *43*



44 + ClTa(O–CMe$_3$)$_4$

catalytic activity of the "tetravalent" tungsten compound **44** (olefin metathesis) is exclusively due to a phosphane dissociation pre-equilibrium and, thus, proceeds immediately in the center of the molecule but does not involve peripheral ligands[46].

8. Closing Remarks—Future Trends

What have we learned in the foregoing discussion? Organometallic model reactions have uncovered numerous, in part entirely new fundamental pathways in synthesis gas chemistry. Moreover, they have provided detailed knowledge of simple organometallic species, *e.g.* formyl and μ-methylene compounds. The mechanistic concept of the Fischer-Tropsch synthesis becomes clearer now in that the reaction principles regarding carbide, methylene, hydroxymethyl, formyl and hydroxycarbene complexes are far better understood than a few years ago. Therefore, unrealistic pathways for synthesis gas reactions can be excluded on the basis of such knowledge. There is increasing evidence that the carbide/methylene mechanism should be considered as offering the best description of reductive oligomerization of carbon monoxide giving oxygen-free products. Since there is no unambiguous proof for the hydrido(carbonyl)→η^1-formyl interconversion, caution has to be exercised in focusing on the participation of formyl intermediates in the chain-growth process, at least from the viewpoint of a critical organometallic chemist, because this important question is lacking a comprehensive, clear answer.

We should not forget that several striking experimental results still await elucidation. For example, all mechanisms that have hitherto been considered by various researchers do not sufficiently explain the fact that increasing H_2/CO pressure ratios favor the formation of alcohols under the conditions of heterogeneous F-T catalysis. In addition, both the participation of the side product water in the initial steps of the Fischer-Tropsch synthesis [eq. (a)] and the possibility of consecutive CO insertion reactions into methylene- and alkyl-metal bonds remain unclear. A comprehensive mechanism for carbon monoxide hydrogenation yielding oxygenates as well as the mechanistic explanation of alcohol homologation processes offer serious problems. Here, model studies involving carbonylation of metallacycles should provide a means of throwing some light on these questions.

Dinuclear μ-methylene complexes will undoubtedly play a pivotal role in further model studies. In this context it should be investigated whether combination of typical Fischer-Tropsch metals (*e.g.* transition metals of group VIII) with the pronounced oxophilic, electron-deficient early transition metals (*e.g.*, group IV and V-metals such as Ti, Nb, and Ta) renders catalytic CO/H_2 reactions possible. Finally, carbide cluster compounds that are nowadays easily accessible require further investigations into their capability for initiating Fischer-Tropsch-type reactions. Immobilized, polymer-supported catalytic centers[41] are expected to demonstrate the borderline between heterogeneously and homogeneously catalyzed synthesis gas reactions and to reveal the importance of multi-site activation in the course of the F-T process. It should prove possible to recognize the interrelationship with other kinds of catalytic reactions such as the olefin metathesis.

At present, considerable interest is attached to the stepwise improvement of heterogeneous catalysts in order to gradually approach the new selectivity goal mentioned in the Introduction. These developments should not have been neglected here; therefore, we conclude our review by pointing out the quintessence of two outstanding papers which nicely demonstrate future trends. Thus, the selectivity for C_2- to C_5-olefins is enhanced from 40 to 55% ($H_2:CO=2:1$; 200 °C) if ruthenium carbonyl, $Ru_3(CO)_{12}$, is used in place of the usual precursors $RuCl_3$ or $Ru(NO)(NO_3)_3$ for the preparation of $Ru/\gamma\text{-}Al_2O_3$ catalysts. Even more informative is the result that addition of the standard promoter potassium to the "$Ru_3(CO)_{12}$"/γ-Al_2O_3 catalyst once again enhances the process selectivity for low molecular weight olefins (80% at 1% K-content); at the same time, the overall activity of the catalyst for CO hydrogenation is found to decrease to a very large extent (*ca.* 50%)[47]. This striking contradictory effect —selectivity *versus* activity— is less pronounced in the case of the conventional "$RuCl_3$"/γ-Al_2O_3 catalyst. From these results, it is suggested that addition of potassium suppresses surface-induced hydrogen dissociation and, at the same time, stabilizes the adsorbed carbon monoxide, thus decreasing the activity for hydrogenation of CO. The enhancement of the olefin selectivity indicates that the surface-anchored alkyl intermediates experience an acceleration in β-hydrogen ab-

straction[47]. Another study has shown that ruthenium/zeolite catalysts (*e.g.*, Ru/zeolon; 3% Ru; Si/Al = 5 : 1) suffer from decreasing activity for syn-gas methanation with increasing acidity of the catalyst support—an observation which directly corresponds to increasing electron-deficiency of the catalytically active metal[48]. These and related findings are certainly interesting for the tailoring of new Fischer-Tropsch catalysts.

The results of my group that have been mentioned in this review arise from the enthusiasm of my coworkers, whose work I greatly appreciate. Generous support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the BASF Aktiengesellschaft, the Hoechst Aktiengesellschaft, the Chemische Werke Hüls, the Degussa Hanau, the Humboldt Foundation, and the Karl-Winnacker Foundation is also gratefully acknowledged.

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Translated by Dr. *J. M. Huggins*, Regensburg

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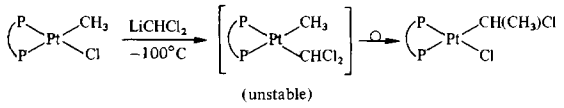

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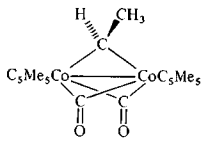

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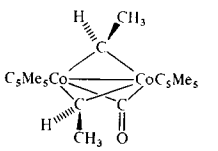

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compounds belonging to this series see W. A. Herrmann, J. M. Huggins, Ch. Bauer, M. Smischek, M. L. Ziegler, H. Pfisterer, *J. Organomet. Chem.* (1982), in press.

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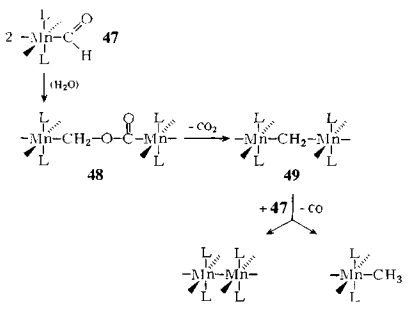
to the following scheme (L = $P(OCH_3)_3$; CO groups omitted for sake of clarity):



The unstable intermediate **48** is postulated in analogy with the formation of an isolable metalloester complex from a formylrhenium precursor [25e]. The μ-methylene species **49** that undergoes subsequent disproportionation appears the most plausible intermediate on the basis of ^{1}H-NMR spectroscopical as well as chemical evidence; e) C. P. Casey, M. A. Andrews, D. R. McAlister, J. E. Rinz, *J. Am. Chem. Soc. 102* (1980) 1927.

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COMMUNICATIONS

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

Umpolung of Carbonyl Reactivity *via* Acetoxyalkyl Radicals**

By *Bernd Giese** and *Ulrich Erfort*

The nucleophilic acetoxy radicals **7** can be generated from ketones **6** *via* the hydrazones **8** by mercuration (**8**→**9**) and reduction (**9**→**7**). The carbonyl carbon atom thus undergoes an umpolung from an acceptor to a donor[5]. Generation of the radicals **7** in the presence of acrylonitrile leads to formation of the product **10** *via* a radical chain mechanism (see Table 1) in a reaction analogous to that of the unsubstituted alkylmercury salts[2].

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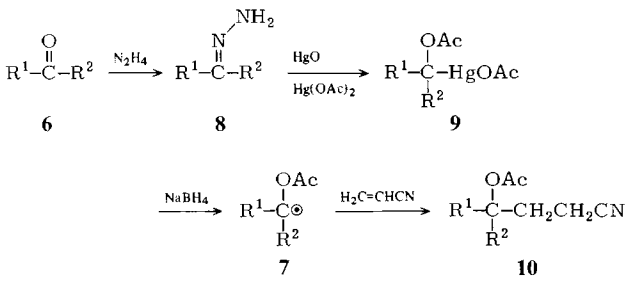

Table 1. Synthesis of **10** by mercuration of hydrazones (**8**→**9**) and reduction in the presence of acrylonitrile (**9**→**10**).

R^1	R^2	Yield **8**→**9** [%]	Yield **9**→**10** [%]
CH_3	CH_3	71	70
CH_3	C_2H_5	61	65
CH_3	i-C_3H_7	35	62
C_2H_5	C_2H_5	45	71
i-C_3H_7	i-C_3H_7	14	33
—$(CH_2)_4$—		54	72
—$(CH_2)_5$—		52	72

In the mercuration step (**8**→**9**) and the radical chain reaction (**9**→**10**) up to 72% yields are obtained. Only upon incorporation of two bulky isopropyl groups are the yields lowered to 14% and 33%, respectively (Table 1). These CC coupling reactions are not limited to acrylonitrile, but can also be performed with ester-, ketone-, anhydride-, phenyl-, or chloro-substituents. In this connection the yields are higher the more rapidly the alkenes react with nucleophilic radicals[7].

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CAS Registry numbers:
8 ($R^1=R^2=$Me), 5281-20-9; **8** ($R^1=$Me, $R^2=$Et), 29443-39-8; **8** ($R^1=$Me, $R^2=i$Pr), 53001-46-0; **8** ($R^1=R^2=$Et), 76291-47-9; **8** ($R^1=R^2=i$Pr), 62104-18-1; **8** (R^1, $R^2=$ —$(CH_2)_4$—), 10080-41-8; **8** (R^1, $R^2=$ —$(CH_2)_5$—), 6156-08-7; **9** ($R^1=R^2=$Me), 80484-09-0; **9** ($R^1=$Me, $R^2=$Et), 80484-10-2; **9** ($R^1=$Me, $R^2=i$Pr), 80484-11-3; **9** ($R^1=R^2=$Et), 80484-12-4; **9** ($R^1=R^2=i$Pr), 80484-13-5; **9** (R^1, $R^2=$ —$(CH_2)_4$—), 80484-14-6; **9** (R^1, $R^2=$ —$(CH_2)_5$—), 80484-15-7; **10** ($R^1=R^2=$Me), 60388-76-3; **10** ($R^1=$Me, $R^2=$Et), 80484-16-8; **10** ($R^1=$Me, $R^2=i$Pr), 80484-17-9; **10** ($R^1=R^2=$Et), 80484-18-0; **10** ($R^1=R^2=i$Pr), 80484-19-1; **10** (R^1, $R^2=$ —$(CH_2)_4$—), 80484-20-4; **10** (R^1, $R^2=$ —$(CH_2)_5$—), 80484-21-5

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Evolution of Hydrogen from Photochemically Reduced Water-Soluble Tin(IV)-Porphyrins

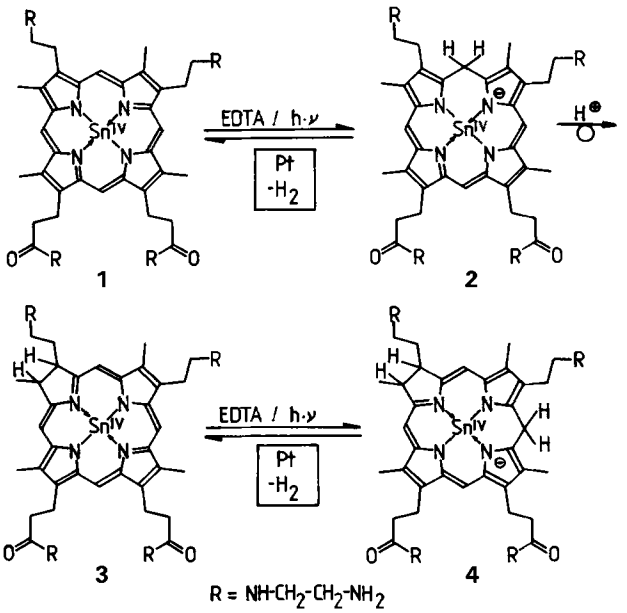
By *Wolfgang Krüger* and *Jürgen-Hinrich Fuhrhop**

The tin(IV) complex **1** of a water-soluble porphyrin[3] was reduced to the green chlorin **3** ($\lambda_{max}=620$ nm) on irradiation with visible light in the presence of ethylenediaminetetraacetic acid (EDTA). The phlorin monocation **2**, which has been detected previously in similar photoreductions[4], is most likely formed as intermediate. On further irradiation the chlorin **3** is converted into the isobacteriochlorin containing two reduced pyrrole rings ($\lambda_{max}=604$ nm).

We have carried out the same photoreduction with a 5×10^{-5} M solution of **1** in presence of colloidal platinum[5] (2×10^{-5} mol/L). **1** was likewise reduced to **3**, but not to the isobacteriochlorin. Moreover, within one hour 10—20 mL of H_2 was formed per liter of solution at pH 4, and 20—30 mL per liter of solution at pH 5. The amount of hydrogen was independent of the conversion **1**→**3**. We assume that the phlorins **2** and **4** act in like manner as hydride-generating molecules. In presence of *N,N'*-dimethyl-4,4'-bi(pyridinium) dichloride (10^{-3} mol/L) the amount of hydrogen remains essentially unchanged (20—40 mL).

At higher or lower pH values, or on replacement of **1** by the analogous zinc porphyrinate, no hydrogen is evolved. After several hours, increasing aggregation of the porphyrin **1** and of the chlorin **3** was observed. No hydrogen was generated in such aged solutions.

The reaction sequence is outlined in the scheme below, where it is seen that a reaction of chlorophyll biogenesis (porphyrin reduction) is coupled with a partial step of photosynthesis (hydrogen formation).



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CAS Registry numbers:
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Bridged $C_5Me_5Co^{II}$ Complexes—Reactive Intermediates in the Cyclopentadienylation of Cobalt(II) Halides**

By *Ulrich Kölle**, *Fouad Khouzami*, and *Bernhard Fuss*

In attempts to synthesize decamethylcobaltocene **1a**[2] we found that the product from $[Co(NH_3)_6]Cl_2$ and

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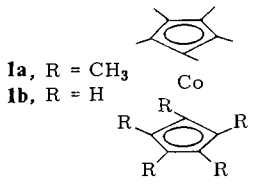
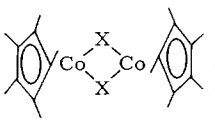
[**] Pentamethylcyclopentadienylmetal complexes, Part 4.—Part 3: U. Kölle, F. Khouzami, *Chem. Ber.*, in press.

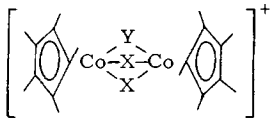
C_5Me_5Li, following *in situ* oxidation with $FeCl_3$, is not the expected pale yellow cation **1a**$^+$, but a violet salt whose properties are consistent with a complex cation of type **3**$^+$ (X = NH_2, Cl).



1a, R = CH_3
1b, R = H



2a, X = Cl
2b, X = Br
2c, X = I
2d, X = NH_2



3a, X = Y = Cl[13]
3b, X = Y = Br
3c, X = Y = I
3d, X = NH_2, Y = Cl

To elucidate the course of the reaction, the Co(II) salts $[Co(NH_3)_6](BF_4)_2$, $CoCl_2$, $CoBr_2 \cdot$ 1,2-dimethoxyethane, and CoI_2 were reacted with C_5Me_5Li (in the molar ratio 1 : 1) as a suspension in tetrahydrofuran at 0—35 °C; thereby, the neutral complexes **2a—2d**, which are soluble in pentane, were obtained. The compositions of **2a** and **2b** were established by elemental analysis; their formulation as dimers stems from the mass spectra of **2a, 2b,** and **2d.** The stability of the complexes decreases along the series X = Cl > Br > $NH_2 \gg$ I, and hence the existence of **2c** can only be deduced from its subsequent reactions with *e.g.* CO to give **4** and **5b.** The complexes **2** are extremely air-sensitive and paramagnetic; ESR data of **2a, 2b,** and **2d** suggest rhombic d^7-systems.

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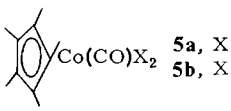
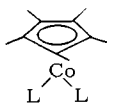
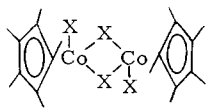


5a, X = Br
5b, X = I



6a, L = C_2H_4
6b, L = 1/2 1,5-Cyclooctadiene
6c, L = 1/2 1,3-Butadiene
6d, L = 1/2 1,2,3,4-Tetraphenylcyclobutadiene



7a, X = Cl
7b, X = Br

The labile compounds **2** can be oxidized by FeY_3 (Y = Cl, Br) or I_2 to give **3** and can be reduced by CO or Na/Hg in the presence of ethylene to give **4** or **6a,** respectively; disproportionation of **2b** and **2c** with CO led to **4** and **5,** while reaction of **2a** and **2b** with 1,5-cyclooctadiene, 1,3-butadiene or tolan yields **6b, 6c,** and **6d,** in addition to **7a** and **7b,** respectively. The reactions proceed spontaneously, at or below room temperature, to give the products in 60 to 90% yield; since the intermediates **2** need not be isolated, these complexes can *de facto* be prepared in a one-pot system from a Co(II) salt, C_5Me_5Li, and another anionic or neutral ligand. The significance of this novel synthetic principle lies in the fact that Co(I) compounds **4**[10] and **6a,** as well as the Co(III) complexes **3**$^+$, **5,** and **7** can be converted into a multiplicity of new Co sandwich and semi-sandwich complexes *via* addition or exchange reactions.

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[2] a) U. Kölle, F. Khouzami, *Angew. Chem. 92* (1980) 658; *Angew. Chem. Int. Ed. Engl. 19* (1980) 640; b) *Chem. Ber. 114* (1981) 2929.
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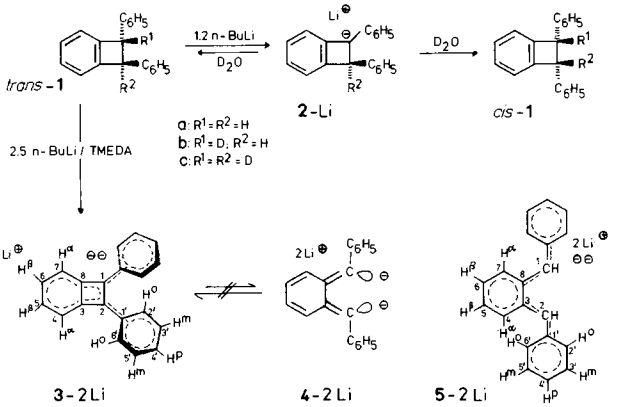
The Dianion 1,2-Diphenylbenzocyclobutadienediide**

By *Gernot Boche*, Heinz Etzrodt, Michael Marsch,* and *Walter Thiel*

Although the series of compounds which should be aromatic according to the Hückel rule have been the subject of numerous intensive studies[2], no convincing proof of the existence of the cyclobutadienediide dianion has so far been reported[2, 7]. What is the reason for this? The two and four additional π-electrons which the dianion has in comparison to the neutral molecule and the dication, respectively, leads to a closed $(4n+2)$ π-electron configuration, but, within the framework of the Hückel approximation, *not to an increase in the π-bonding energy.* Thus, the strong electron repulsion in a planar $C_4H_4^{2\ominus}$ could become the domineering destabilizing factor, similarly as the ring strain in cyclodecapentaene[2].

Further information in this respect is afforded by the dilithium salt of the 1,2-diphenylbenzocyclobutadienediide **3**-2Li, which we prepared by reaction of *trans*-**1a** with 2.5 equiv. of *n*-BuLi/tetramethylethylenediamine (TMEDA) (1 : 1) in tetrahydrofuran. With *n*-BuLi alone only the monoanion **2**-Li is formed, which on reaction with D_2O yielded *cis*- and *trans*-**1b**; **3**-2Li was deuteriated with D_2O to *cis*- and *trans*-**1c.** That the latter was not formed from **4**-2Li and D_2O followed from the ^{13}C-NMR spectrum of the dianion solution: The signals of C^1 and C^2 appear at $\delta = 83.8$; in the case of **4**-2Li the signals would have appeared much further downfield. Moreover, according to MNDO calculations, $\mathbf{4}^{2\ominus}$ is about 20.7 kcal/mol less stable than $\mathbf{3}^{2\ominus}$.



The bonding situation in **3**-2Li was investigated NMR spectroscopically, the open-ring dianion **5**-2Li serving as suitable reference substance.

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[**] This work was supported by the Fonds der Chemischen Industrie. We thank Prof. *H. Günther,* Siegen, and Prof. *G. Maier,* Giessen, for helpful discussions.

From the ^{13}C-NMR spectrum of **3**-2Li empirically derivable charges ρ_{emp}[19d] are obtained which are in good agreement with the calculated MNDO charges of $3^{2\ominus}$. A comparison of the $\delta(^{13}C)$- and ρ_{emp}-values of the two dianions shows that the electron density distributions in the cyclic **3**-2Li and in the acyclic **5**-2Li are almost the same. Furthermore, in **3**-2Li only about 48% of both charges appear in the benzocyclobutene moiety. Thus, a preferred cyclic delocalization with formation of an aromatic $(4n+2)$ π-electron system is not observed in the case of **3**-2Li.

Analysis of the ^{1}H-NMR spectrum using a method described by *Günther et al.*[20d], in which the benzene ring in **3**-2Li serves as a probe for the properties of the attached annulene, led to the same result. Thus, the "Alternanzparameter" Q for **3**-2Li (1.05) is reconcilable only with an "olefinic" and not with an "aromatic" π-system in the four-membered ring.

The low acidity of **2**-Li, the electron distribution in **3**-2Li, and the Q-value of **3**-2Li preclude the latter dianion being designated as an aromatic compound. **3**-2Li is preparable because the negative charges are largely taken over by the substituents. This reduces unfavorable electron repulsion in the four-membered ring.

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[2] Summary: P. J. Garratt in S. D. Barton, W. D. Ollis: *Comprehensive Organic Chemistry*, Pergamon Press, Oxford 1979, Vol. 1, p. 215 and 361.
[7] G. Maier, F. Köhler, *Angew. Chem. 91* (1979) 327; *Angew. Chem. Int. Ed. Engl. 18* (1979) 308 (and further references cited therein and in [1]).
[19] d) H. Baumann, H. Olsen, *Helv. Chim. Acta 63* (1980) 2202.
[20] d) H. Günther, M. E. Günther, D. Mondeshka, H. Schmickler, F. Sondheimer, N. Darby, T. M. Cresp, *Chem. Ber. 112* (1979) 71.

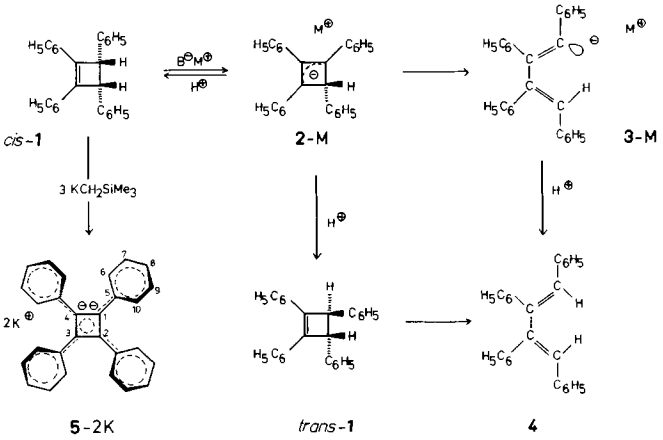
The Dianion 1,2,3,4-Tetraphenylcyclobutadienediide**

By *Gernot Boche**, *Heinz Etzrodt*, *Michael Marsch*, and *Walter Thiel*

Lack of information on the cyclobutadienediide dianion (cf. [1]) induced us to re-attempt the synthesis of the tetraphenylcyclobutadienediide dianion $5^{2\ominus}$[2]. In the following communication we report on the access to and the properties of **5**-2K.

Previous attempts[2] to prepare **5**-2M from *cis*-**1** and bases ($B^{\ominus}M^{\oplus}$) had led with *n*-BuLi in tetrahydrofuran (THF) to the stable lithium salt of the monoanion **2**-Li, and with KO*t*Bu in dimethyl sulfoxide *via* **3**-K to **4**. Reaction of *cis*-**1** with KO*t*Bu or lithium dicyclohexylamide in THF had afforded **4** *via trans*-**1**. The same was observed with lithium diisopropylamide, lithium *tert*-butylcyclohexylamide and lithium tetramethylpiperidide in THF; *n*-BuLi/tetramethylethylenediamine and *t*BuLi in THF, on the other hand, led to **2**-Li and to addition of base at the stilbene double bond.

Only the strongest base known at present, namely $(CH_3)_3SiCH_2K$[5], in THF led to **5**-2K. Reaction with D_2O, giving dideuterio-*cis*- and dideuterio-*trans*-**1** proved the presence of the dianionic four-membered ring. This ruled



out the presence of the valence isomer of **5**-2K corresponding to **3**-M and **4**, the 1,4-dipotassio-1,2,3,4-tetraphenylbutadiene **6**-2K, as an alternative. Nevertheless, according to MNDO calculations $6^{2\ominus}$ is only 11.2 kcal/mol less stable than $5^{2\ominus}$.

The NMR spectra of the dianion confirm the presence of **5**-2K: ^{13}C-NMR: $\delta = 108.8$ (C^{1-4}), 141.9 (C^5), 122.9 ($C^{6,10}$), 127.7 ($C^{7,9}$), 112.8 (C^8); ^{1}H-NMR: $\delta = 6.93$ (d, $H^{6,10}$), 6.61 (t, $H^{7,9}$), 5.97 (t, H^8).

Furthermore, it follows from the NMR spectra that the phenyl groups take over a considerable part of the negative charges. Thus, the charges ρ_{emp}[1], which can be determined from the ^{13}C-NMR spectrum, and which correlate with the calculated ρ_{MNDO} charges, indicate that only about 36% of the two negative charges are found on the four-membered ring C-atoms. Also consistent with this conclusion is the calculated MNDO π-bond order of 0.470 for the exocyclic bonds (*e.g.* C^1—C^5), whereas a bond order of only 0.450 is obtained for the bonds in the four-membered ring.

The exceptionally low acidity of **2**-M, the calculated enthalpies of formation ΔH_f, and the charge distribution obtained from the NMR data do not characterize **5**-2K as "aromatic"[1, 12b]. It can be concluded from these results that the unsubstituted cyclobutadienediide dianion must be still more energy-rich and more basic than **5**-2K, because stabilization by delocalization of charge(s) in the phenyl groups is missing there.

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Novel Chlorooxoaluminates**

By *Ulf Thewalt** and *Friederike Stollmaier*

The reductive Friedel-Crafts synthesis of arene-transition metal complexes generally leads to formation of salt-like compounds containing arene-metal cations and chlo-

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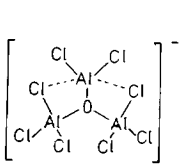
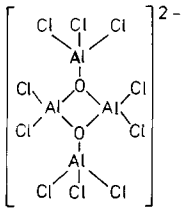
roaluminate anions[1]. By means of X-ray structure analyses we have now been able to characterize products containing chlorooxoaluminate ions. The complex compounds $[(C_6H_6)(C_6(CH_3)_6)Cr]^+[Al_3Cl_8O]^- \cdot 1/2\,C_6H_6$[2a] and $[(C_6(CH_3)_6)_2Nb_2Cl_4]^{2+}[Al_4Cl_{10}O_2]^{2-} \cdot 2\,CH_2Cl_2$[4a], both of which are extremely sensitive to hydrolysis, contain the



1



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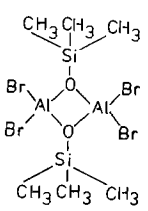

3

novel anions **1** and **2**, in which the O-atoms are surrounded by an almost trigonal-planar arrangement of Al-atoms. In **1** a distorted trigonal-bipyramidal coordination is realized for one of the Al-atoms. The axial Al—Cl distances (2.63 and 2.73 Å) are markedly greater than the equatorial Al—Cl distances (2.07 and 2.07 Å) The structure of **2** is analogous to that of the X-ray crystallographically characterized[6] alumosiloxane **3.**

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Angew. Chem. Suppl. 1982, 209-213

[1] E. O. Fischer, H.-P. Fritz, *Angew. Chem. 73* (1961) 353.
[2] a) The compound is formed in small amounts along with other products in the reaction of $CrCl_3$, $AlCl_3$, Al and $(CH_3)_6C_6$ in benzene in a bomb-tube at 120 °C (13 h).
[4] a) The compound is formed, along with other compounds, when the product prepared by melting together $NbCl_5$, $(CH_3)_6C_6$, $AlCl_3$ and Al is dissolved in CH_2Cl_2 and the solution briefly exposed to air.
[6] M. Bonamico, G. Dessy, *J. Chem. Soc. A 1967*, 1786.

Rotation of Polymerized Vesicles in an Alternating Electric Field**

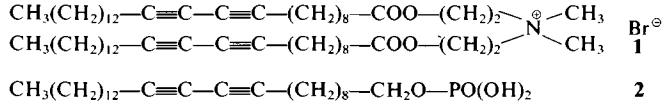
By *Hans-Henning Hub, Helmut Ringsdorf,* and *Ulrich Zimmermann**

Suspended cells rotate at certain frequencies in alternating electric fields[1a]. The frequency ranges in which suspended cells rotate are species-specific and/or membrane-specific (*e.g.* 20—40 kHz for mesophyll protoplasts of *Avena sativa,* 100—200 kHz for erythrocytes, 140—180 kHz for yeast cells, 30—40 kHz for permanent cell lines, and 1 MHz for plant protoplasts and erythrocytes treated with pronase). The rotation (about 1 rotation/s) is a function of the square of the field intensity[1]. Theoretically, it can be attributed to an interaction between induced dipoles in neighboring cells. Maximum coupling between the neighboring dipoles occurs when the cells are oriented at an angle of 45° to each other[1b]. Rotation of a free cell is, therefore, not possible if the cell is far enough away from the electrodes and other cells (however, see[2]). Dipole-dipole interaction between two neighboring cells leads to a mean torque different from zero.

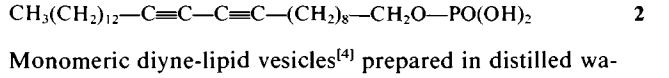
Maximum torque occurs when $\omega\tau = 1$ (τ is the relaxation time of the dipole build-up and ω is the angular frequency). According to theory[1b], the number of rotating cells should, therefore, progressively decrease towards higher and lower frequencies.

On the other hand, our studies of erythrocytes, plant protoplasts, and permanent cell lines have revealed that cell rotation can be induced in the frequency range 70—140 MHz. The discrepancy between theory and experiment can be explained if it is assumed that various relaxation mechanisms underlie the build-up of a dipole in cells. Dipoles may be, induced, *inter alia*, by the orientation of the phospholipids and/or proteins in the membrane or by charge separation at the membrane. The relaxation time, τ, can be calculated for the latter mechanism[3].

Systems such as polymeric diyne-lipid vesicles (from lipid **1** or **2**), which are homogeneous and have fixed components, should therefore exhibit only one frequency range for maximum rotation, since dipoles can only be built up by charge separation.



1



2

Monomeric diyne-lipid vesicles[4] prepared in distilled water at 70 °C and polymerized afterwards, were exposed to an alternating field of 100 kHz between two parallel cylindrical electrodes glued to a microscope slide. Because of the inhomogeneity of the field the vesicles migrate towards the region of higher field intensity (*i.e.* towards the electrodes) and form "pearl chains" as a result of the forces of attraction between the dipoles induced in the vesicles by the field[1]. If several parallel pearl chains are formed, many vesicles are oriented at an angle of 45° to each other. Rotation of the vesicles is observed in the frequency range 1—4 MHz. As predicted by theory, no rotation was observed outside this frequency range up to 170 MHz or down to 10 kHz (minimum output voltage of the high frequency generator 3-5 V, electrode distance 100 μm). No experiments could be carried out in the frequency range 40—70 MHz because of resonance in the experimental system.

According to theory[3], the frequency at which all vesicles rotate is displaced to higher values when the intra- and/or extravesicular conductivity of the vesicles is increased. Polymeric vesicles prepared and incubated in a 10^{-3} M KCl solution exhibited the predicted shift towards higher frequency (7—15 MHz). No rotation was observed in the remaining, experimentally accessible frequency range. If the intravesicular KCl concentration was raised to 10^{-2} M KCl no rotation was observed in the entire frequency range. The reason for this observation may be that the membranes become permeable so that charge separation can no longer take place.

These results demonstrate that the rotation observed in the range 20 kHz—3 MHz in different cell types is very probably attributable to charge separation. Rotation of cells in the 100 MHz range must thus be attributable to an orientation of dipoles within the membrane or to the occurrence of rotating fields in this frequency range. If it were possible to determine and assign the respective specific frequencies for the orientation of these components in the high frequency range using artificial lipid vesicles of various compositions and fluidities, *the determination of*

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the rotational spectrum could become an important tool in cell and membrane research. The experimental result that rotation ceases when the membrane permeability is increased may explain why electrically induced fusion of monomeric vesicles is observed only occasionally and not reproducibly. In permeable membranes the breakdown voltage can no longer be reached so that fusion cannot be initiated. For the purpose of electric field induced fusion, the occurrence of rotation in an alternating field thus represents an accessible criterion for the integrity of biological and artificial membranes.

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Stereoselectivity and Relative Reactivity in the Reaction of Organotitanium and -zirconium Reagents with Carbonyl Compounds**

By *Manfred T. Reetz*, Rainer Steinbach, Jürgen Westermann, Ralf Urz, Bernd Wenderoth,* and *Roland Peter*

Organotitanium and -zirconium compounds[1a,b,2a,c] such as **1**—**6** react far more selectively than their lithium-, magnesium- and zinc analogues.

$RTi(O\text{-}i\text{-}C_3H_7)_3$
1a, R = CH_3
1b, R = CD_3
1c, R = n-C_4H_9
1d, R = CH_2=$CHCH_2$

$CH_3Ti(OC_2H_5)_3$ **2**

$R_2Ti(O\text{-}i\text{-}C_3H_7)_2$
3a, R = CH_3
3b, R = CD_3

$Ti(CH_3)_4$ **4**

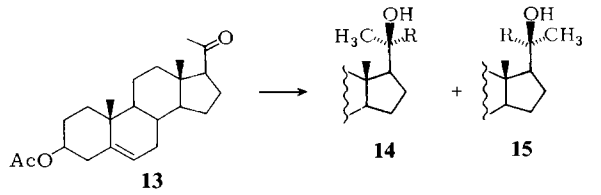
$CH_3Zr(O\text{-}n\text{-}C_3H_7)_3$ **5**

$Zr(CH_3)_4$ **6**

Addition of **1a, 1c, 2, 4,** and **5** to 2-phenylpropanal leads preferentially to the "Cram products" (*erythro* : *threo* up to 93 : 7). Other zirconium reagents react similarly, whereas the analogous lithium and magnesium reagents display far less diastereodifferentiation ($\approx$2 : 1).

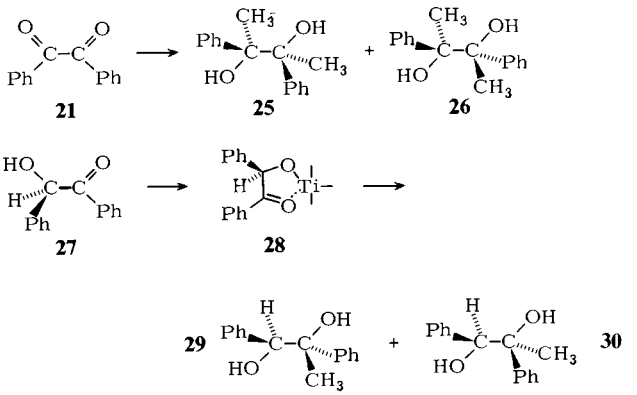
Asymmetric induction in the construction of steroid side chains can be realized particularly easily with titanium reagents, but not with zirconium reagents. Reaction of **13** with **1d** or **1b** leads to formation of the diastereomers **14a** and **15a** or **14b** and **15b** in the ratio >90 : 10 and 96 : 4, respectively. Furthermore, a titanium enolate derived from *O*-methylestrone undergoes an *erythro*-selective aldol addition, whereby practically only one of the four possible diastereomers is formed.

In order to test whether *Cram*'s "cyclic model" is applicable in the case of titanium and zirconium reagents, benzil **21** was allowed to react with **1a, 2, 3** or **4** to give **25** (*d,l*~*threo*) + **26** (*meso*~*erythro*) (>98 : 2, 60 : 40, 93 : 7 and 98 : 2, respectively). This is a *reversal* of the 1,2-asymmetric induction observed on reaction with **5**, methyllithium or methylmagnesium bromide (**25** : **26** in the ratios of 19 : 81, 15 : 85, and 28 : 72 respectively) and thus supports *Anh*'s open-chain model[5]. Reaction of **27** with **1a** or **4** yields exclusively the *erythro* isomer (**29** : **30** in the ratio >99 : 1), indicating intermediary formation of the sterically less strained chelate **28.**



13 **14** **15**

a, R = CH_2=$CHCH_2$; **b**, R = CD_3



21 **25** **26**

27 **28**

29 **30**

Noticeable 1,3- and 1,4-asymmetric induction is observed on addition of **1a** and **4** to 3-hydroxybutyraldehyde or phthalaldehyde (diastereomeric ratios up to 70 : 30 and 83 : 17, respectively).

The rate of addition of the reagents to ketones decreases along the series **4**$\approx$**6**>**3**>**1a**$\approx$**5**. In the titanium series itself: allyl > methyl > *n*-butyl. The *highly reactive but not very basic tetramethylzirconium* **6** adds to sterically highly hindered compounds, particularly in cases in which methyllithium, **1a** or **5** fail. Titanium or zirconium reagents react selectively with ketones in the presence of ester groups, but lactonization can occur.

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[1] a) M. T. Reetz, J. Westermann, R. Steinbach, *Angew. Chem. 92* (1980) 933; *Angew. Chem. Int. Ed. Engl. 19* (1980) 902; b) M. T. Reetz, R. Steinbach, J. Westermann, R. Peter, *ibid. 92* (1980) 1044 or *19* (1980) 1011.
[2] a) B. Weidmann, D. Seebach, *Helv. Chim. Acta* **63** (1980) 2451; c) B. Weidmann, C. D. Maycock, D. Seebach, *ibid. 64* (1981) 1552.
[5] N. T. Anh, *Top. Curr. Chem. 88* (1980) 40.

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O,O-Dialkylthiophosphonosulfenyl Bromides—A New Class of Reactive Organophosphorus Compounds

By *Jan Michalski*, Marek Potrzebowski,* and *Andrzej Łopusiński*

We report that the reaction of elemental bromine with dithiophosphoric acid derivatives **1** (X = H) leads to a new

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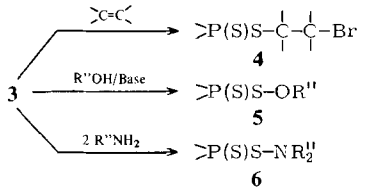
class of compounds, the sulphenyl bromides **3**, in quantitative yield. The reaction proceeds *via* the disulphides **2**, which can be used advantageously as educts. The bromides **3** are also formed in quantitative yield by the action of Br_2 on trimethylsilyl esters **1** ($X = SiMe_3$).

$$\underset{\mathbf{1}}{2\,RR'P(S)SX} \xrightarrow[-2XBr]{Br_2} \underset{\mathbf{2}}{RR'P(S)SS(S)PRR'} \xrightarrow{Br_2} \underset{\mathbf{3}}{2\,RR'P(S)SBr}$$

a, $R = R' = tBuCH_2O$; **b**, $R = R' = iPrO$; **c**, $R = R' = MeO$; **d**, $R = R' = PhO$; **e**, $R = tBu$, $R' = MeO$

By analogy, *O*-methyl butyldithiophosphonate **1e** ($X = H$) reacts to give **3e**. The sulfenyl bromides **3** can be isolated in a pure state[1], but decompose at room temperature (within a few days) to the bromides RR'P(S)Br and sulfur.

The bromides **3** react readily at room temperature or below with various nucleophiles giving a variety of novel or difficultly accessible organophosphorus compounds.



Compounds of type **5** react with trimethylsilyl chloride to give in high yield sulfenyl chlorides **7** which, due to their reactivity, are suitable educts for the synthesis of other organophosphorus compounds[2].

$$\underset{\mathbf{5}}{RR'P(S)S{-}OR''} + ClSiMe_3 \rightarrow \underset{\mathbf{7}}{RR'P(S)SCl} + R''OSiMe_3$$

Experimental[1]

3c: A solution of Br_2 (1.6 g, 10 mmol) in 5 mL of CCl_4 was added to a stirred solution of **2c** (3.14 g, 10 mmol) in 10 mL of CCl_4 at $-25\,^\circ C$. Solvent was removed at 0—5 °C/5 torr, yielding **3c** (4.7 g) as a yellow oil. **3c** could be added to cyclohexene in CH_2Cl_2 at 0 °C to give the 2-bromocyclohexyl compound $(MeO)_2P(S)SC_6H_{10}Br$ (type **4**) in 88% yield; b.p. = 105—108 °C/0.01 torr, ^{31}P-NMR (C_6H_6): $\delta = +97$.

7a: Me_3SiCl (1.3 g, 12 mmol) was added to a stirred solution of **5a** (3.5 g, 10 mmol) ($R = R' = R'' = tBuCH_2O$) in 20 mL of CH_2Cl_2 at $-10\,^\circ C$, and the mixture stirred for 20 min at $-5\,^\circ C$. After removal of the solvent and trimethylsilyl ether at 0 °C under reduced pressure, **7a** (3.0 g) was obtained; ^{31}P-NMR (CH_2Cl_2): $\delta = +79.5$. **7a** reacts with piperidine to give the piperidide (m.p. = 67 °C) in 86% yield.

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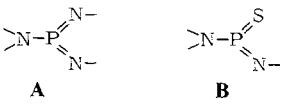
[1] All the new compounds were characterized by elemental analysis and ^{31}P-NMR spectroscopy (standard: ext. H_3PO_4); ^{31}P-NMR: **3a**, $\delta = +74.7$; **3b**, $\delta = +70.7$; **3c**, $\delta = +79.9$; **3d**, $\delta = +69.8$; **3e**, $\delta = +110.7$.

[2] a) L. Almasi, A. Hantz, *Chem. Ber. 97* (1964) 661; L. Almasi, L. Paskucz, *ibid. 98* (1965) 3546; b) L. Almasi, A. Hantz, *Monatsh. Chem. 99* (1968) 1045, and references cited therein; c) A. Łopusiński, J. Michalski, W. J. Stec, *Justus Liebigs Ann. Chem. 1977*, 924.

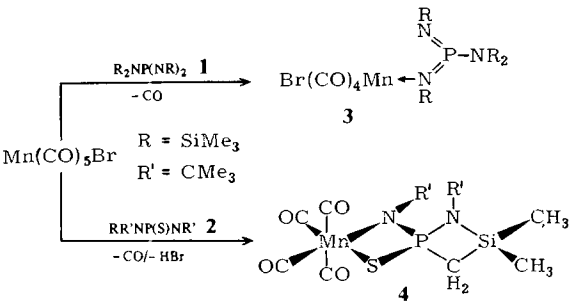
Manganese Complexes with "End-On" and Spirocyclic Bonded σ^3,λ^5-Phosphazene Ligands**

By *Otto J. Scherer**, *Jürgen Kerth*, *Barbara K. Balbach* and *Manfred L. Ziegler*

Until now the complex chemistry of σ^3,λ^5-phosphazenes **A** [aminobis(imino)phosphoranes] and **B** [amino(imino)thiophosphoranes] has been limited to two reaction types.



Whereas the double ylide **A** reacts with, *e.g.*, $TiCl_4$[1] or $(C_3H_5)_2Pd$[2] to give the transition metal chelate complexes $L_xM(NR)_2PR'R''$ with a four-membered ring framework, obtainable with platinum by other means[3], reaction of **B** with $(Ph_3P)_2Pt(C_2H_4)$ led to "side-on" coordination of the P=S group[4]. We have now found that with $R_2N{-}P(=NR)_2$ **1**, $Mn(CO)_5Br$ forms the complex **3** which contains an "end-on" bonded σ^3,λ^5-phosphazene ligand, while with $RR'N{-}P(S){=}NR'$ **2**, it forms the phosphorus spiro compound **4** whose ring framework consists of two four-membered rings each of which contains four different elements.



3 can be isolated from hexane as permanganate-colored, extremely air-sensitive crystals which are readily soluble in ether, benzene, *n*-hexane, and dichloromethane. In solution, **3** exhibits dynamic behavior: the intramolecular exchange of the $Br(CO)_4Mn$ moiety from one to the other imino group, which at room temperature occurs rapidly on the NMR time scale, is measurably slowed down at low temperatures ($\Delta G_c^{\neq} = 51\ kJ \cdot mol^{-1}$)[6]. When **3** and Ph_3P (molar ratio 1:2) are warmed for 2.5 h at 40 °C in hexane, uncoordinated double ylide **1** is formed in high yield together with a mixture of *fac*-$Mn(CO)_3(PPh_3)_2Br$ [*ca.* 80%: ^{31}P-NMR (CD_2Cl_2, $-50\,^\circ C$): $\delta = 35.2$(s)] and *mer*-$Mn(CO)_3$-*ce*-$(PPh_3)_2Br$ [*ca.* 20%; ^{31}P-NMR: $\delta = 54.5$ (s)].

4 forms yellow-brown, slightly air-sensitive crystals from ether which are readily soluble in CH_2Cl_2 and CH_3CN, moderately soluble in ether and benzene, and sparingly soluble in *n*-hexane. The NMR data (*e.g.* the four expected singlets from the CO groups are found in the $^{13}C\{^1H\}$ spectrum) of **4**, as well as the X-ray structure analysis confirm the tetrahedral environment of the P atom.

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The angle between the S—P—N(1) and C—P—N(2) planes is 92.9°. In contrast to the planar ring containing the Si atom, the other ring is puckered (angle between the planes S—Mn—N(1) and S—P—N(1) = 20.8°).

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[1] E. Niecke, R. Kröher, S. Pohl, *Angew. Chem. 89* (1977) 902; *Angew. Chem. Int. Ed. Engl. 16* (1977) 864.
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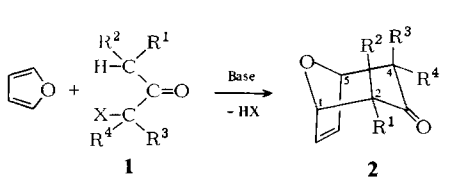
[6] ^{1}H-NMR [$C_6D_5CD_3$; −60°C: δ = 0.45 (s, 18H), 0.22 (s, 9H), −0.17 (s, 9H); 20°C: δ = 0.45 (s, 18H), 0.24 (s, 18H)]. ^{31}P{^{1}H}-NMR [$C_6D_5CD_3$; −60°C as well as 20°C: δ = −1.6 (s)]. ^{13}C{^{1}H}-NMR [$C_6D_5CD_3$; −60°C: δCO = 227 (s); the appearance of a single CO signal is an indication of a *trans*-configuration in **3**]. IR [*n*-hexane; metalcarbonyl region: ν = 2030 (s), 1935 (vs), 1904 (w) cm^{-1}].

Efficient Synthesis of 8-Oxabicyclo[3.2.1]oct-6-en-3-ones, Preparatively Useful [4+3]-Cycloadducts**

By *Baldur Föhlisch**, *Eberhard Gehrlach*, and *Rolf Herter*

The title compounds **2**, accessible by cycloaddition of allylium-2-olates to furans have proven to be valuable educts for the synthesis of natural products and biologically active analogues. Previously, however, the cycloadducts could only be synthesized using tedious and expensive methods[2a,3a,4,5,7]. We have now found a method in which not only α-bromoketones but also the less expensive and more stable α-chloroketones can be reacted with readily available bases.

The α-haloketones **1a–h** react with furan in 2,2,2-trifluoroethanol (TFE), a very weakly nucleophilic and powerful ionizing solvent, in the presence of triethylamine or sodium 2,2,2-trifluoroethoxide generated *in situ* to give 8-oxabicyclo[3.2.1]oct-6-en-3-ones **2** (Table 1). The yields are good, and work-up is simple. The bicyclic compounds **2b—f** are formed stereoselectively. By reduction of **2f** or **2g** with the Zn/Cu couple, the unsubstituted ketone **2**, $R^1 - R^4 = H$, is also accessible in good yields. α-Chloroketones can not only be prepared by chlorination of ketones, but also *via* several other routes, by C—C coupling reactions. Thus, the [4+3]-cycloaddition of allylium-2-olates opens up promising applications in synthetic chemistry.



1 **2**

	R^1	R^2	R^3	R^4	X		R^1	R^2	R^3	R^4	X
a	CH_3	CH_3	H	H	Cl	**e**	CH_3	CH_3	H	CH_3	Cl
b	CH_3	H	H	CH_3	Cl	**f**	Cl	Cl	H	Cl	Cl
c	CH_3	H	H	CH_3	Br	**g**	Cl	Cl	Cl	Cl	Cl
d	CH_3	H	CH_3	CH_3	Cl	**h**	H	—$(CH_2)_3$—		H	Br

Table 1. 8-Oxabicyclo[3.2.1]oct-6-en-3-ones **2** by reaction of α-haloketones **1** and furan in TFE/furan (1:1 v/v) at room temperature with triethylamine (Method A: molar ratio 1:2) or sodium trifluoroethoxide (Method B: molar ratio 1:1) as base. All products except **2g** are known.

Educt 1	Method	Reaction time	Product 2	Yield [%]	*T* [°C/torr] [a] M.p. [°C]
a	A	25 d	**a**	45	120–140/12
a	B	29 d	**a**	56	41–42
b	A	5 d	**b** [b]	77	120–140/12
b	B	6 d	**b** [b]	80	33–35
c	B	1 d	**c** ≡ **b** [b]	93	
d	A	4 d	**d**	73	130–150/12
d	B	3 d	**d**	91	70–90/0.3
e	A	10 d	**e** ≡ **d**	68	13–16
f	A	75 min	**f**	55	70–90/0.001 88–89
g	A	75 min	**g** [c]	52	90–120/0.001 88–89
h	A	1 d	**h**	84	60–70/0.002 43–44

[a] Kugelrohr temperature. [b] The product contains at maximum 6% of the C-2/C-4 epimers. M.p. of isomerically pure **2b**: 45–46°C. [c] ^{1}H-NMR ($CDCl_3$): δ = 5.25 (s, 1-H, 5-H), 6.65 (s, 6-H, 7-H); IR ($CHCl_3$): 1765 cm^{-1} (C=O).

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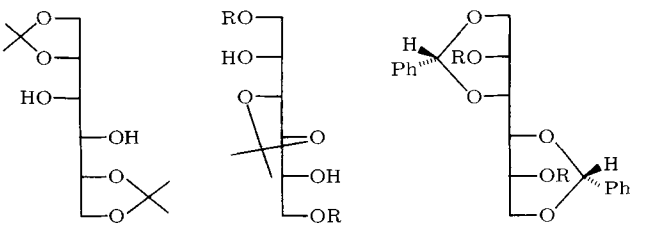
Optically Active Glycerol Derivatives from 1,3(*R*):4,6(*R*)-Di-*O*-benzylidene-D-mannitol—The First Structural Analogues of Moenomycin A**

By *Thomas Schubert* and *Peter Welzel**

Morpain and *Tisserand* recently reported[5] that optically active glycerides are accessible from D-mannitol derivatives of type **2** in fewer steps than from the "classical" educt **1**[1]. Presumably, di-*O*-benzylidene compound **3** is



1 **2**

3, R = H
4, R = $C_{18}H_{37}$
5, R = $C_{20}H_{41}$

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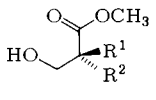
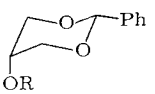
an even better starting material. Certain types of optically active glycerol derivatives can be prepared from **3** with a minimum of protecting group chemistry. Starting from **3** we have synthesized **6** and **7**, as well as **15**, a structural analogue of the antibiotic moenomycin A[6].

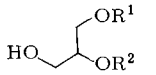
Alkylation of **3**[8] with 1-bromooctadecane or with 2,3-dihydrophytyl bromide in dimethylformamide afforded **4** (81%) and **5** (70%), respectively. Hydrolytic cleavage of the benzylidene protecting groups, followed by diol cleavage with sodium metaperiodate, subsequent oxidation of the aldehyde with silver(II) oxide and esterification of the resulting acid then furnished the *R*-glyceric acid derivatives **6** (36%) and **7** (56%), respectively.



6, R^1 = H, R^2 = $OC_{18}H_{37}$
7, R^1 = H, R^2 = $OC_{20}H_{41}$
8, R^1, R^2 = H, $OC_{18}H_{37}$



9, R = H
10, R = $C_{18}H_{37}$

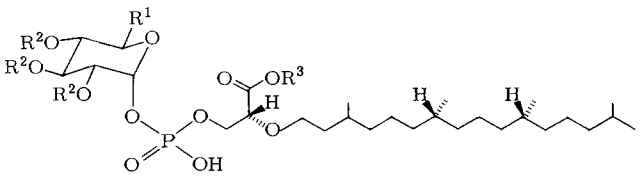


11, R^1 = COC_6H_5, R^2 = $C_{18}H_{37}$
12, R^1 = $COCH_3$, R^2 = $C_{18}H_{37}$

The racemic ester **8** was synthesized from *cis*-5-hydroxy-2-phenyl-1,3-dioxane **9**. *O*-Alkylation with 1-chlorooctadecane (phase-transfer catalysis) furnished **10** in 67% yield. Deslongchamps opening[14] of **10** to the hydroxybenzoate **11**, Jones oxidation, and esterification of the acid afforded the racemic ester **8** (51%, referred to **10**). **8** is also accessible in a total yield of 61% from **10** by hydrolytic cleavage of the benzylidene group, monoacetylation to **12**, Jones oxidation, and subsequent esterification.

In presence of the optically active shift reagent Eu(tfc)$_3$ the ^{1}H-NMR spectrum of **8** shows two OCH_3 signals (ratio: 1 : 1), while the spectrum of **6** recorded under the same conditions shows only one: hence, within the limits of NMR detection, **6** is formed in optically pure form.

For the preparation of **15**, **7** was allowed to react with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl 1-phosphate according to the phosphoric acid diester method using 2,4,6-triisopropylbenzenesulfonyl chloride to give the diester **13**. Cleavage of the protecting groups with lithium hydroxide yielded the dilithium salt of **14**, which was converted by catalytic oxidation into the glucuronic acid derivative **15** (after ion-exchange).



13, R^1 = CH_2OAc, R^2 = Ac, R^3 = CH_3
14, R^1 = CH_2OH, R^2 = H, R^3 = H
15, R^1 = COOH, R^2 = H, R^3 = H

The antibiotic moenomycin A is one of the most active inhibitors of bacterial cell-wall biosynthesis[6]. However, a correlation between its very complex structure and biological activity has thus far been lacking. The synthetic access to model substances such as **15** now opens up the possibility of investigating this problem experimentally.

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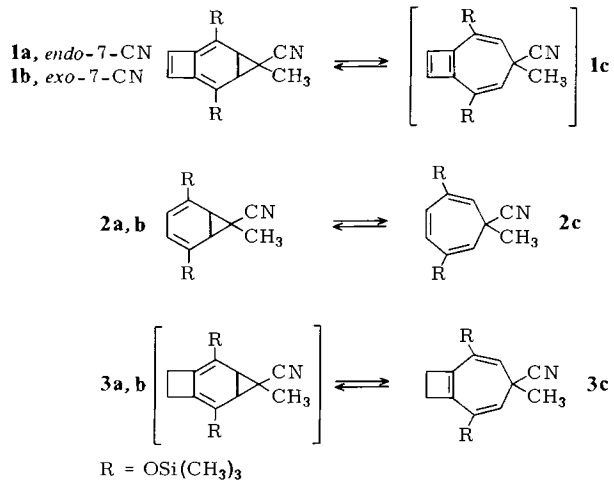
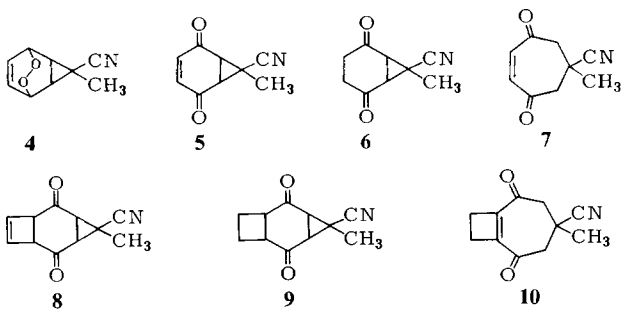
The Effect of an Annelated Cyclobutene or Cyclobutadiene Ring on the Norcaradiene—Cycloheptatriene Equilibrium**

By *Frank-Gerrit Klärner**, *Eckhart K. G. Schmidt*, and *Mahmoud Abdel Rahman*

The question of the antiaromaticity of 1,3-cyclobutadiene has been the subject of repeated theoretical and experimental investigations[1]. In the valence tautomeric equilibrium **1a, b** ⇌ **1c**, the cycloheptatriene derivative **1c** contains a cyclobutadiene ring as a subunit. Provided that cyclobutadiene is antiaromatic, the equilibrium is expected to be shifted in favor of the norcaradienes **1a** and **1b**. We report here on the syntheses and properties of the systems **1, 2,** and **3.**



The syntheses of **1, 2,** and **3** start from 7-methyl-1,3,5-cycloheptatrien-7-carbonitrile[3]. Addition of $^1O_2$ leads to **4** (yield 96%), which on subsequent reduction ($(NH_2)_2CS$ or Pt/H_2) and oxidation (MnO_2 or CrO_3) is converted into **5** (64%) or **6** (54%), respectively. Photochemical addition of



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ethyne or ethene to **5** affords **8** (97%) or **9** (93%), respectively. On reaction of compounds **6**, **8**, and **9** with CF_3SO_3—$Si(CH_3)_3$[5], the enol ethers **2**, **1**, and **3**, respectively, are obtained in yields of 80, 75, and 80%.

According to the ^{1}H-NMR spectra measured between +50 °C and −100 °C, **1** has the structure of the norcaradiene derivative **1a**, and **3** of the cycloheptatriene derivative **3c**. **2** consists of a mixture of **2a**, **2b**, and **2c** (equilibrium ratio, at −90 °C, 52 : 41 : 7); at room temperature the equilibration **2a** ⇌ **2c** ⇌ **2b** is rapid on the NMR time scale ($\Delta G^{\neq}$ values between 10 and 14 kcal/mol). Spectroscopic assignment is confirmed by the secondary reactions of **1**, **2**, and **3**. Hydrolysis of the enol ether functions of **1** leads only to regeneration of **8**. In the case of **2** and **3**, on the other hand, only the respective diketones **7** and **10** formed from **2c** and **3c** are obtained. Consequently, the rapid valence isomerization observed in the other systems **2a** and **3a** does not take place in the norcaradiene **1a**, either under conditions of formation or hydrolysis. This is due to the destabilizing effect of the annelated cyclobutadiene ring in the cycloheptatriene derivative **1c**.

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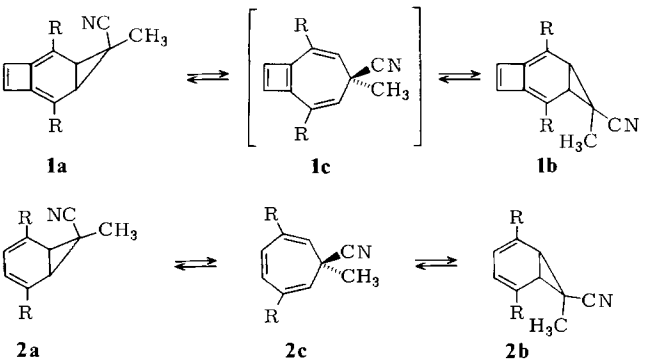
The Question of the Antiaromaticity of 1,3-Cyclobutadiene: Thermal Valence Isomerization of the Tricyclo[5.2.0.0^{3,5}]nona-1,6,8-triene System**

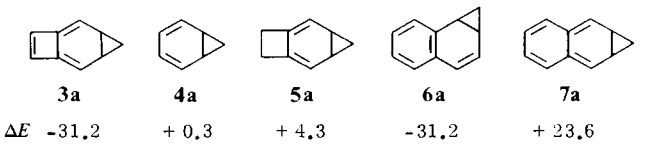
By *Frank-Gerrit Klärner**, *Eckhart K. G. Schmidt*, *Mahmoud A. Abdel Rahman*, and *Herbert Kollmar*

Negative resonance energy is frequently cited as a criterion of antiaromaticity. Values between 0 and −33 kcal/mol have been calculated for cyclobutadiene[2c]; the data derived from experiments vary between −11 and −16 kcal/mol[2c]. We report here on the negative resonance energy of cyclobutadiene, which follows from a study of the equilibria **1a** ⇌ **1c** ⇌ **1b** and **2a** ⇌ **2b** ⇌ **2c**. Unlike **2a**[4], the norcaradiene **1a** rearranges to the diastereoisomer **1b** up to the equilibrium ratio (70 : 30) only on heating (60 °C). The ^{1}H-NMR spectroscopically determined activation parameters for the isomerization **1a** ⇌ **1b** still do not give any direct information about the position of the equilibria **1a** ⇌ **1c** and **1b** ⇌ **1c**. For the valence isomerizations **1c** → **1a**, **1c** — **1b**, and **2c** → **2a**, **2c** — **2b** which are of the same type similar activation barriers can be assumed to a first approximation. From the kinetic data given in Scheme 1 the norcaradienes **1a** and **1b** can be estimated to be each *ca.* 14 kcal/mol more stable than the cycloheptatriene derivative **1c**.

In order to determine the antiaromaticity of the unsubstituted cyclobutadiene, the additional effects of the conjugated systems (3,4-dimethylenecyclobutene and 1,2-divinylcyclobutadiene) occurring in **1a** or **1b** and **1c** must be considered. According to an *ab initio* SCF calculation (5.2/2, minimal base)[2a, 2b] 3,4-dimethylenecyclobutene has a small negative resonance energy (−2.7 kcal/mol), while 1,2-divinylcyclobutadiene is favored by resonance by about 4 kcal/mol in comparison to the components cyclobutadiene and 1,3,5-hexatriene. Adding these corrections to the experimentally derived value a negative resonance energy of *ca.* −21 kcal/mol is obtained for cyclobutadiene, which is of the same order of magnitude as the positive resonance energy of benzene.



Scheme 1. Thermal valence isomerizations of the norcaradiene derivatives **1a** and **2a**. $k_{1a,1b}$ (60 °C) = (3.6 ± 0.1) × 10^{-5} s^{-1}, $\Delta G^{\neq}$ = 26.3 kcal/mol; $k_{1b,1a}$ (60 °C) = (8.3 ± 0.5) × 10^{-5} s^{-1}, $\Delta G^{\neq}$ = 25.8 kcal/mol. **2a** → **2c** (−54 °C): $\Delta G^{\neq}$ = 11.5; **2c** → **2a** (−54 °C): $\Delta G^{\neq}$ = 10.7; **2b** → **2c** (−15 °C): $\Delta G^{\neq}$ = 13.3; **2c** → **2b** (−15 °C): $\Delta G^{\neq}$ = 12.4.



Scheme 2. *Ab initio* SCF energy values (ΔE in kcal/mol) of the norcaradienes **3a** to **7a** (relative to the corresponding (not shown) cycloheptatrienes **3c** to **7c**) [2a, b].

A comparison of the experimental and calculated energy values for **1a** and **3a** and for **6a**[7b] shows that the influence of antiaromaticity, like that of aromaticity, is overestimated from the calculation.

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C-Carboxylation of Nitroalkanes with 1-Ethoxycarbonylbenzotriazole

By *Mladen V. Proštenik** and *Ivan Butula*

The synthetic utility of *C*-carboxylation of simple nitroalkanes for the preparation of 2-nitrocarboxylic acid es-

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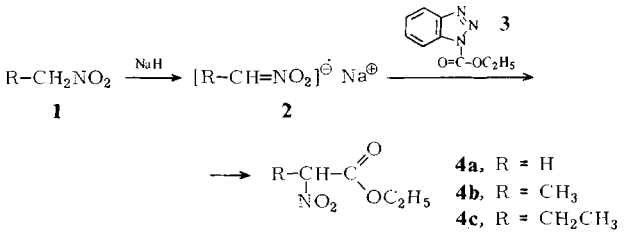
ters **4** is low because of the low nucleophilicity of the anionic species, which has a strong tendency to *O*-carboxylation. An exception is the dilithium salts $[R{-}C{=}NO_2]^{2\ominus}2Li^{\oplus}$ which are carboxylated by various reagents[6].



$$R{-}CH_2NO_2 \xrightarrow{NaH} [R{-}CH{=}NO_2]^{\ominus}\,Na^{\oplus} \xrightarrow{O{=}C{-}OC_2H_5}$$

1 **2**

$$\longrightarrow R{-}\underset{NO_2}{\underset{|}{CH}}{-}\overset{O}{\overset{\|}{C}}{-}OC_2H_5$$

4a, R = H
4b, R = CH_3
4c, R = CH_2CH_3

We now report the *C*-carboxylation of the sodium salts **2** of nitroalkanes **1** with 1-ethoxycarbonylbenzotriazole **3**, in which the electrophilicity of the carbonyl C atom is increased by the presence of the benzotriazole moiety. In this reaction, the nitroesters **4a—4c** were obtained at 30 °C from **1** (R = H, CH_3, C_2H_5) in 55—80% yield in dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) as solvent using sodium hydride as base. In tetrahydrofuran or dioxane the reaction proceeds with lower conversions, even at higher temperatures. Nitro(phenyl)methane cannot be carboxylated in this way.

The present method for preparation of nitroesters **4** offers advantages over existing procedures in terms of simplicity, ease of work-up, and yields[3–5]. The reagent **3** is easy to prepare[7] and can be regenerated from the liberated benzotriazole.

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Electron Transfer by Grignard Reagents: Direct Evidence for Organomagnesium Radical Complexes

By *Wolfgang Kaim**

Electron transfer mechanisms are increasingly being invoked to describe the reactions of alkylmetal compounds with organic substrates[1]. The formation of radical ions in the reaction of electron deficient compounds with Grignard reagents has frequently been reported[5]; however, the nature of these paramagnetic species has remained uncertain[5].

Investigations of the reducibility of pyrazines[6] have now shown that these compounds react with RMgX or R_2Mg in ethers to give persistent radicals whose ESR parameters deviate significantly from those of the "free" radical anions (Table 1).

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Reaction of pyrazine with Grignard reagents produces radicals having complex ESR spectra with nonequivalent nuclei. Addition of an alkali metal to this solution results in the observation of the spectrum (Fig. 1 B) of a symmetrical species. At high resolution, apart from the ^{13}C satellite coupling (4C), the interaction of the unpaired electron with two magnesium nuclei in natural abundance can be detected.

Table 1. ESR coupling constants a_i [mT] of organomagnesium radical complexes [a].

Radical	a_N	a_H^{CH}	a^{25}_{Mg}	a^{13}_{C}
$Pz^{\cdot-}$	0.718	0.264	–	0.288
$[Pz(MgC_2H_5)]\cdot$	0.684	0.272 0.304 [b]	[c]	[c]
$[Pz(MgC_2H_5)_2]^{\cdot+}$	0.685	0.284	0.029	0.31
$[Pz(MgC_6H_5)]\cdot$	0.680	0.260 0.310 [b]	[c]	[c]
$[Pz(MgC_6H_5)_2]^{\cdot+}$	0.677	0.285	0.036	0.33
$[(Me_4Pz)(K)]\cdot$	0.618	0.173 [d]	–	[c]
$[(Me_4Pz)(MgC_6H_5)_2]^{\cdot+}$	0.595	0.192 [d]	0.024	[c]

[a] Pz = pyrazine; Me_4Pz = tetramethylpyrazine. [b] Coupling constants of nonequivalent nuclei. [c] Not observed. [d] Methyl proton coupling constants.

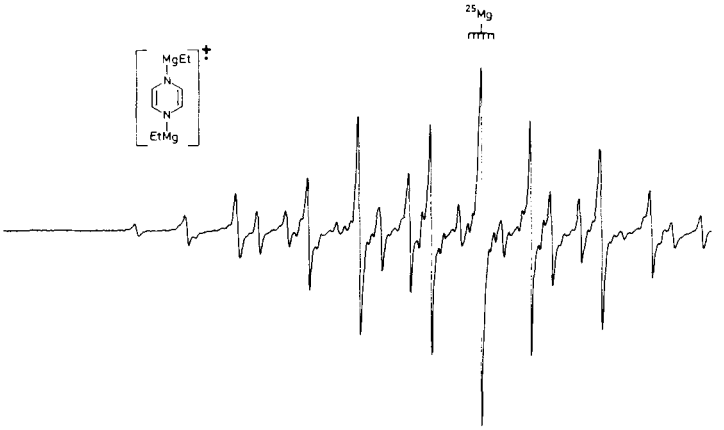
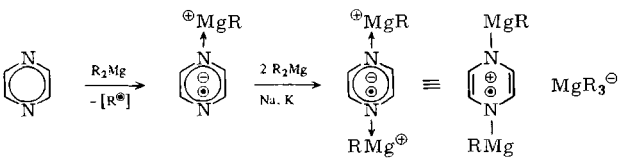


Fig. 1 B). Part of the ESR spectrum of the radical complex formed in the reaction of pyrazine with diethylmagnesium and potassium in tetrahydrofuran (THF). The ^{25}Mg satellites of the most intense line are indicated (^{25}Mg: $I = 5/2$, 10%).

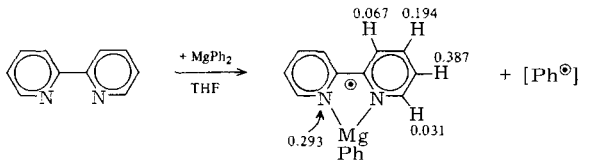
The description of the radical complexes is supported by the interpretation of analogous organoaluminum[6a] and organosilicon coordination compounds[6b]. Favored by the dissociation of organomagnesium compounds in ether[10],

$$2\,R_2Mg \rightleftharpoons RMg^{\oplus} + R_3Mg^{\ominus}$$

an acceptor RMg^+ initially coordinates to the reduced form of pyrazine resulting from electron transfer; reduction by alkali metal leads to coordination of RMg^+ to *both* N atoms.



A highly persistent radical can also be obtained from Grignard reagents and the chelate-forming 2,2′-bipyridyl (ESR coupling constants in mT).



The reaction of Grignard reagents with readily reducible oxygen compounds, *e.g.* ketones, should be interpreted analogously: The observed radical "intermediates"[5] would then be formulated as radical anion-organometallic cation complexes.

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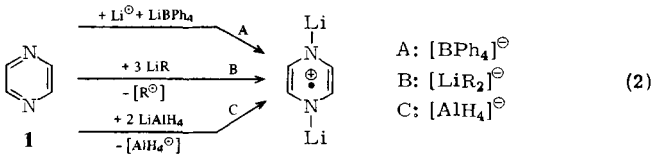
[1] Cf. J. K. Kochi: *Organometallic Mechanisms and Catalysis*, Academic Press, New York 1978; E. C. Ashby, *Pure Appl. Chem. 52* (1980) 545.
[5] Note added in proof: A recent communication on the reaction mechanism of the reduction of aromatic ketones by Grignard reagents did not contain an analysis of the ESR spectra. The formulation of the paramagnetic species as "radical anion-radical cation pairs" is inconsistent with the apparent doublet character of the observed radicals: E. C. Ashby, A. B. Goel, *J. Am. Chem. Soc. 103* (1981) 4983.
[6] a) W. Kaim, *J. Organomet. Chem. 201* (1980) C 5; *215* (1981) 325, 337; b) *Angew. Chem. 92* (1980) 940; *Angew. Chem. Int. Ed. Engl. 19* (1980) 911; c) *ibid. 93* (1981) 620, 621 and *20* (1981) 599, 600; *Inorg. Chim. Acta 53* (1981) L51; *Z. Naturforsch. B 36* (1981) 677.
[10] W. Strohmeier, F. Seiffert, *Z. Elektrochem. Ber. Bunsenges. Physik. Chem. 63* (1959) 683.

Ambivalent Coordination Behavior of Lithium Aluminum Hydride in Electron Transfer Reactions

By *Wolfgang Kaim**

Recent studies[1] have demonstrated the important role of electron transfer mechanisms in the reactions of organometal and hydridometal compounds with reducible organic substrates. N-Heterocycles such as pyrazine **1** can be advantageously used as "electron transfer traps"[11], because complete reduction would lead to an unfavorable electron configuration[8]; the radical ion intermediates are thus detected by stationary methods (ESR, UV). With the heterocycles pyrazine **1**, quinoxaline **2** and 4,4'-bipyridine **3** as substrates in the electron transfer reaction with the complex hydride $LiAlH_4$ we have now found that the metal coordination exhibits remarkable ambivalence. **1** reacts with $LiAlH_4$ as well as with LiR *via* electron transfer to yield radical "triple ions"[12] with two coordinated lithium ions.



(2)

R = CH_3, n-C_4H_9, C_6H_5

In contrast, the radical anions $2^{\ominus}$ and $3^{\ominus}$ do not employ the Li^+ but the H_2Al^+ cations as coordinated metal species. The ESR parameters of these radical complexes agree well with the data of corresponding dimethylaluminum complexes (Table 1).

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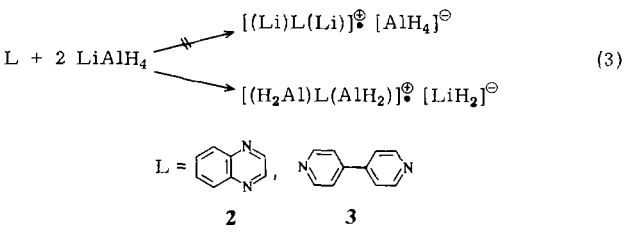
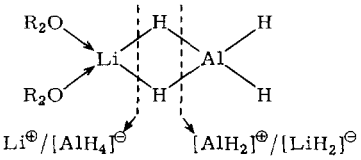


(3)

Table 1. ESR coupling constants a [mT] of organoaluminum radical complexes.

	$[2(AlX_2)_2]^{\ominus\bullet}$ X = H	X = CH_3 [10]		$[3(AlX_2)_2]^{\ominus\bullet}$ X = H	X = CH_3 [10]
a_N	0.618	0.611	a_N	0.347	0.352
$a_{H_{2,3}}$	0.380	0.368	a_{H_2}	0.099	0.096
$a_{H_{5,8}}$	0.120	0.120	a_{H_3}	0.198	0.192
$a_{H_{6,7}}$	0.120	0.120	a^{27Al}	0.149	0.128
a^{27Al}	0.238	0.203	a_H^{AlH}	≤0.020	—
a_H^{AlH}	0.028	—			

The ambivalent coordination behavior of $LiAlH_4$ is a result of its structure in solution; an arrangement such as (4) allows two reasonable polar dissociation mechanisms.



(4)

Whereas reduced pyrazines show a distinct propensity to form ion pairs or triple ions with alkali metal cations[12], corresponding complexes have not been reported for the less basic radical anions $2^{\ominus}$ and $3^{\ominus}$. Therefore, in the electron transfer reaction with $LiAlH_4$ their preference is for the stronger coordinating[10] H_2Al^+ ions.

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[1] J. K. Kochi: *Organometallic Mechanisms and Catalysis*, Academic Press, New York 1978; cf. also *Chem. Eng. News 59* (1981) No. 15, p. 26; No. 30, p. 38.
[8] W. Kaim, *Angew. Chem. 93* (1981) 620; *Angew. Chem. Int. Ed. Engl. 20* (1981) 599.
[10] W. Kaim, *J. Organomet. Chem. 215* (1981) 325, 337.
[11] W. Kaim, *Angew. Chem. 94* (1982) 150; *Angew. Chem. Int. Ed. Engl. 21* (1982) 140; *Z. Naturforsch. B36* (1981) 1110; *J. Organomet. Chem. 222* (1981) C17.
[12] Cf. S. A. Al-Baldawi, T. E. Gough, *Can. J. Chem. 49* (1971) 2059.

Stereospecific Synthesis of (*S,S*)-Palythazine from D-Glucose**

By *Pan Jarglis* and *Frieder W. Lichtenthaler**

Apart from the exceedingly poisonous palytoxin[2] and a number of cyclohexanoid iminium salts such as palythene and palythinol, the invertebrate salt water animal *Palythoa tuberculosa* produces two heterocycles with the novel dipy-

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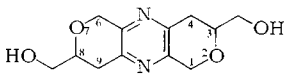
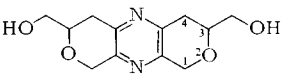
[**] Sugar Enolones, Part 15.—Part 14: [8].

ranopyrazine skeleton, for which structures **1** ("palythazine") and **2** ("isopalythazine") have been delineated on the basis of analytical, UV, and NMR evidence[4]. Their absolute configurations, however, have not yet been established.



1



2

For each of these hexahydrodipyranopyrazines three configurational isomers are possible, *i.e.* an (*R,R*)- an (*S,S*)-, and a *meso*-form of which the latter can be ruled out, since **1** as well as **2** are optically active[4]. We chose to answer the question of whether the *Polythoa* containing **1** has an (*R,R*)- or (*S,S*)-configuration by synthesizing (*S,S*)-**1** stereospecifically *via* sugar enolones[6] by unambiguous derivation of both chiral centers from the configuration at C-5 of D-glucose.

The tetra-*O*-benzoyl derivative **3**, readily accessible from D-glucose, undergoes selective hydroxylaminolysis[8] resulting in cleavage of the enol ester function to give, in essentially quantitative yield, the ketoxime **4**, which with acetaldehyde is readily converted into the parent ketose **5** (Scheme 1).

Due to the high propensity of peracylated pyranosuloses to eliminate acyloxy functions β to the carbonyl group[6], the conversion **5**→**6** is effected cleanly under mild conditions. When subjected to standard deacylation conditions (Scheme 1), enolone **6** yields a complex product mixture due to concomitant aldol type condensations and/or benzilic acid rearrangements of the liberated diketone; in contrast, the benzoyl protecting groups in oxime **7** are readily cleaved off on of the hydroxyimino group providing the nitrogen functionality required in consecutive steps, as well as protection of the carbonyl group against condensation reactions[9].

8 can be converted by controlled catalytic reduction into the aminoketone **9**, which undergoes self-condensation under Gutknecht conditions; oxidation of the tricyclic dihydropyrazine formed gives **1**. The resulting (57% overall yield for 3 steps) (*S,S*)-palythazine **1** is highly crystalline, has a high melting point (223—225 °C after sublimation at *ca.* 190 °C), exhibits a high negative rotation ($[\alpha]_D^{25}$ −199°, methanol), and gives ^{1}H- and ^{13}C-NMR data in accord with the hexahydrodipyranopyrazine structure.

Comparison of synthetic (*S,S*)-**1** with the *Palythoa tuberculosa*-derived product[4] has mainly been confined to the melting points, since rotational data were not disclosed[4]. Surprisingly, the melting point of synthetic **1** closely corresponds to that reported for the natural isopalythazine **2** (216—219 °C[4]), and differs markedly from that given for palythazine **1** (169—170 °C[4]). This indicates that the structures of the *Palythoa* pyrazines have been incorrectly assigned, *i.e.* that the high melting isomer has the structure of palythazine **1** while the low melting isomer has that of **2**. Support for this interpretation is derived from the fact that the ^{13}C-NMR data reported for **1** and **2**[4] are so similar as to preclude unambiguous differentiation.

In relation to biogenesis of **1** and **2**, it appears not unlikely that *Palythoa tuberculosa* synthesizes these products from D-glucose through a series of oxidation and transamination reactions, conceivably involving **9** as intermediate.

If so, the (*S,S*)-**1** synthesized not only constitutes the natural polythazine but the strategy followed for its synthesis parallels its biosynthesis to a significant extent.

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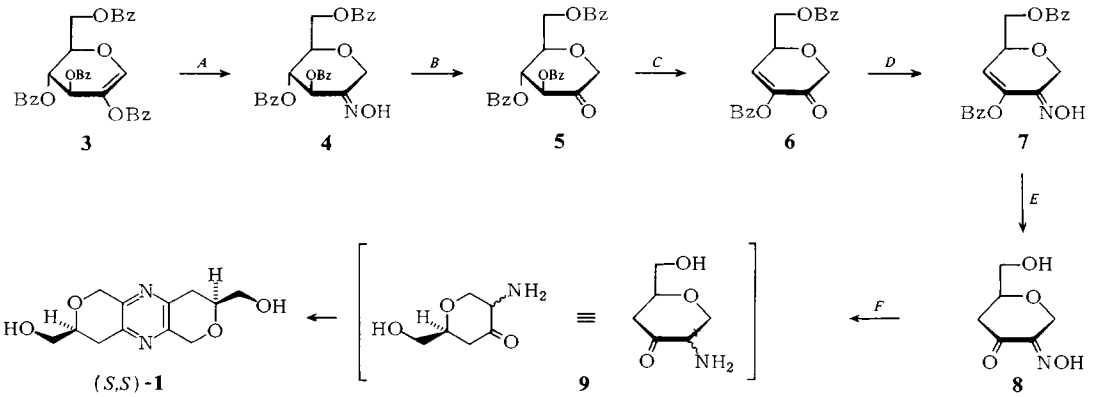
[2] For most recent reports on its structure, cf. R. E. Moore, G. Bartolini, *J. Am. Chem. Soc. 103* (1981) 2491; D. Uemura, K. Ueda, Y. Hirata, H. Naoki, T. Iwashita, *Tetrahedron Lett. 22* (1981) 2781.
[4] D. Uemura, Y. Toya, I. Watanabe, Y. Hirata, *Chem. Lett. 1979*, 1481.
[6] F. W. Lichtenthaler, *Pure Appl. Chem. 50* (1978) 1343.
[8] F. W. Lichtenthaler, P. Jarglis, *Tetrahedron Lett. 21* (1980) 1425.
[9] F. W. Lichtenthaler, E. S. H. El Ashry, V. H. Göckel, *Tetrahedron Lett. 21* (1980) 1429.



Scheme 1. *A:* 3 equiv. $NH_2OH \cdot HCl$/pyridine, 10 h, 70 °C or 4 d, 25 °C (93%); *B:* acetaldehyde/HCl in CH_3CN, 6 h, 25 °C (88%); *C:* NaOAc in acetone, 30 min, 25 °C (92%); *D:* $NH_2OH \cdot HCl$/pyridine in $CHCl_3$/EtOH (5:3), 15 h, 25 °C (96%); *E:* $NaOCH_3/CH_3OH$, −10 °C (89%); *F:* H_2/10% Pd, C in EtOH plus 2 equiv. HCl, after uptake of 2 mol H_2, neutralization, and stirring in air (57%).—Abbreviation: Bz = benzoyl.

Metal Hexamethoxides**

By *Eberhard Jacob**

$U(OCH_3)_6$ **1** is interesting as a substrate for the enrichment of uranium 235 by multiphoton dissociation with a CO_2 laser[2]. Since the compound is accessible only with difficulty, we attempted a direct synthesis from UF_6 *via* ligand exchange. By analogy, as yet unknown metal hexa-

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[**] Low temperature Co-Condensation of Fluorine Compounds, Part 5. Dr. *W. Storch*, Universität München is thanked for valuable discussions.—Part 4 [1].

methoxides should also be able of being synthesized in this way.

The volatile $Si(OCH_3)_4$ **2** was selected as ligand carrier. UF_6 reacts with excess **2** as a solid co-condensate at $-196\,^{\circ}C$ with partial, and after warming with complete ligand exchange (IR thin film spectrum!) The method is also suitable for conversions on the preparative scale (molar ratio of the educts 1 : 10)

$$\underset{\mathbf{2}}{UF_6} + 6\,Si(OCH_3)_4 \xrightarrow[100\%]{\mathbf{2}} \underset{\mathbf{1}}{U(OCH_3)_6} + 6\,\underset{\mathbf{3}}{SiF(OCH_3)_3}$$

and after pumping off the methoxysilanes **2** and **3**, pure **1** is obtained.

Under similar conditions ReF_6 reacts with **2** to give a crimson solution from which the previously unknown $Re(OCH_3)_6$ **4** was isolated (yield 80%); since **4** is volatile in high vacuum at room temperature, it can be separated from by-products by sublimation. The analogous reaction of MoF_6 yielded for the first time $Mo(OCH_3)_6$ **5** and because of the equilibrium

$$MoF(OCH_3)_5 + \mathbf{2} \rightleftharpoons \mathbf{5} + \mathbf{3}$$

only proceeds to completion if **3** is removed during the reaction by pumping. WF_6 reacts with **2** in the absence of marked heat of reaction (co-condensation not required), accordingly

$$WF_6 + 5\,\mathbf{2} \rightarrow \underset{\mathbf{6}}{WF(OCH_3)_5} + 5\,\mathbf{3}$$

The tungsten compound **6** is liquid (m.p. $< -10\,^{\circ}C$) and reacts only partially with **2** to give $W(OCH_3)_6$ **7**[11], *i.e.* the position of the equilibrium is more unfavorable for exchange of the last fluorine ligand than in the case of the molybdenum compound. Complete methoxylation of **6** can be achieved with a methanolic $NaOCH_3$ solution; **7** can be isolated by vacuum sublimation. In general, metal hexamethoxides are volatile solids which are readily soluble in non-polar solvents. Under reduced pressure **6** can be distilled at 60—80 °C, whereas, hereby, the corresponding molybdenum compound[9] decomposes. The ^1H- and ^{13}C-NMR spectra in solution suggest equivalent methoxy groups. The vibrational spectra are dominated below 600 cm^{-1} by the skeletal vibrations of the MO_6 octahedra. The Raman spectra of solid **5** and **7** differ little from those of their solutions. Thermal stability decreases along the series $\mathbf{7} \gg \mathbf{1} > \mathbf{5} > \mathbf{4}$. Thermolysis of **1**, **4**, and **5** at 85 °C led to slow formation of $CH_2(OCH_3)_2$, a little $(CH_3)_2O$, and CH_3OH as cleavage products. In moist-air rapid hydrolysis ensues (particularly with **1** and **4**). The colored compounds **1**, **4**, and **5** are light sensitive. **5** and **7** act as methoxide acceptors. In the reaction with F_2, metal oxide fluorides, COF_2, and HF are formed.

By means of the low temperature co-condensation technique[6], the dominant oxidative fluorinating activity of UF_6, ReF_6, and MoF_6 can be suppressed in favor of an exchange reaction. Methoxy groups are sufficiently electronegative and sterically undemanding to be able to stabilize high oxidation states—for example Re^{VI}. The route presented here has general applications.

Table 1. Physical properties of metal hexamethoxides.

		$U(OCH_3)_6$ **1**	$Re(OCH_3)_6$ **4**	$Mo(OCH_3)_6$ **5**	$W(OCH_3)_6$ **7**
M.p.	[°C]	69.1 ± 0.4	59.0 ± 1.0	67.6 ± 0.4	43.0 ± 0.2
Vapor pressure (25 °C)	[μbar]	≈5	≈30	3	24
NMR [a]	δ^1H	3.78	4.65	4.64	4.52
	$\delta^{13}C$	71.89	[b]	63.82	61.09
IR [e]	ν_3 [c]	466	580	578	546
	ν_3 [d]	443	537	535	—
	ν_1	495.5 [g]	—	568	586
Raman [e]	ν_2	400.6 [g]	—	455	475
	ν_5	—	—	306	306
MS [f]		$U(OCH_3)_5^+$	$Re(OCH_3)_5^+$	$Mo(OCH_3)_5^+$	$W(OCH_3)_5^+$
Color		deep red	brown	golden yellow	colorless

[a] In CCl_4 solution, TMS + C_2D_6 intern. [b] Due to the paramagnetic broadening (δ^1H) or non-measurability ($\delta^{13}C$) of the resonance frequency. [c] Argon matrix, 10 K. [d] Thin film, −60 °C. [e] Fundamental vibrations of the MeO_6 skeleton (cm^{-1}). [f] Fragments with greatest mass. [g] Ref. [2].

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[1] E. Jacob, *Z. Anorg. Allg. Chem. 433* (1977) 255.
[2] S. S. Miller, D. D. DeFord, T. J. Marks, E. Weitz, *J. Am. Chem. Soc. 101* (1979) 1036.
[6] Care! With stacked condensed layers there is a risk of explosion upon thowing due to possible local excess of hexafluoride. The co-condensation technique offers a safe procedure of avoiding this (cf. [9]).
[9] D. W. Walker, J. M. Winfield, *J. Fluorine Chem. 1* (1971/72) 376.
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Peptide Formation by Activation with Phenyltetrazolinethione/Isocyanide**

By *Ulrich Schmidt** and *Manfred Dietsche*

Dedicated to Professor Werner Reif on the occasion of his 60th birthday

ω-Hydroxyacids react with phenyltetrazolinethione and isocyanide to give a mixture of *N*- and *S*-acyltetrazoles, which can be used for the formation of macrocyclic lactones[1]. This activation is also particularly suitable for peptide formation. Z- or Boc-amino acids[2] are allowed to react with the adduct **1** of phenyltetrazolinethione and an isocyanide in concentrated solution at −40 °C. The mixture of *N*- and *S*-acyl compounds of type **2** thus formed already reacts very rapidly at −40 °C on addition of an amino acid ester to give the dipeptide ester in good yields (see Table 1).

In the dipeptide formation corresponding to the first Weygand test[3a] (formation of TFA-Val-Val-OMe[2] as well as formation of Z-Val-Val-OMe and conversion into TFA-Val-Val-OMe) and the third Weygand test[3b] (formation of TFA-Pro-Val-Pro-OMe), in each case at −40 °C, no trace of a racemization could be detected, even by capillary gas-chromatography. No allo-isoleucine compounds are

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[**] Carboxy Group Activation, Part 3; Amino Acids and Peptides, Part 35. This work was supported by the Fonds der Chemischen Industrie and by BASF AG. Part 2: U. Schmidt, M. Dietsche, *Angew. Chem. 93* (1981) 786; *Angew. Chem. Int. Ed. Engl. 20* (1981) 695; Part 34: U. Schmidt, A. Lieberknecht, H. Griesser, J. Talbiersky, *J. Org. Chem.*, in press.

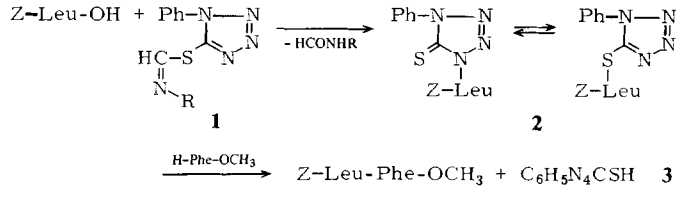

Table 1. Dipeptides by activation with phenyltetrazolinthione/isocyanide.

S,S-Dipeptide	Yield [%]	Optical rotation	*c*	Solvent
Z-Leu-Phe-OMe [5]	84	$[\alpha]_D^{20}$ −27.4	1.3	methanol
Z-Phe-Val-OMe	79	$[\alpha]_D^{25}$ −16.0	2	ethanol
Z-Leu-Leu-OMe	76	$[\alpha]_D^{25}$ −34.9	1	ethanol
Z-Val-Ala-OMe	78	$[\alpha]_D^{22}$ −47.5	1.65	methanol
Z-Ile-Val-OMe	64	$[\alpha]_D^{20}$ −33.8	1.5	methanol
Z-Pro-Val-OMe	80	—	—	—
Z-Aib-Ile-OMe	63	$[\alpha]_D^{23}$ + 2.5	1.28	ethanol
Z-Ile-Aib-OMe	60	$[\alpha]_D^{20}$ + 5.0	2	ethyl acetate

formed during the synthesis of Z-Ile-Aib-OMe and Z-Aib-Ile-OMe[4].

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[1] U. Schmidt, M. Dietsche, *Angew. Chem. 93* (1981) 786; *Angew. Chem. Int. Ed. Engl. 20* (1981) 771.

[2] Z = Benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl, TFA = tetrafluoroacetyl.

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[5] *Procedure:* A solution of phenyltetrazolinethione (980 mg, 5.5 mmol) is treated with cyclohexyl isocyanide (600 mg, 5.5 mmol) at room temperature and the mixture stirred until all is in solution (*ca.* 10 min). After cooling to −40 °C the solution is treated with a cold solution of Z-Leu-OH (1325 mg, 5 mmol) in CH_2Cl_2 (5 mL) and after 2 min with a cold solution of H-Phe-OMe (896 mg, 5 mmol) in CH_2Cl_2 (5 ml). The mixture is warmed to room temperature, diluted with CH_2Cl_2 and extracted several times with 0.5 N NaOH, then with water, 0.5 N $KHSO_4$ and water. The washed solution is evaporated to dryness and the residue taken up in ethyl acetate, filtered through a silica gel column and the solvent removed; yield: 1786 mg Z-Leu-Phe-OMe (84%).—For the synthesis of peptides which are also very sensitive to sodium hydroxide (extraction of phenyltetrazolinethione) in organic solvents, 1-(*m*-dimethylaminophenyl)tetrazolinethione is used for the activation, and can be extracted with dilute acids (preparation from *m*-dimethylaminophenyl isocyanate (R. Zahradník *et al., Collect. Czech. Chem. Commun. 28* (1963) 1651) and sodium azide).

Alkylchromium(III) Dichlorides, Highly Selective Reagents for the Addition of Nucleophiles to Aldehydes**

By *Thomas Kauffmann**, *Angelika Hamsen*, and *Christoph Beirich*

Owing to the preparative significance of CC-coupling by reaction of carbanionic or carbanionoid compounds with electrophiles the finding that the carbanionoids $Cl_3Ti—CH_3$ and $(i\text{-}C_3H_7O)_3Ti—Alk$ (Alk = CH_3, $n\text{-}C_4H_9$) as alkylating reagents distinguish very selectively between aldehydes and ketones[1] is of great importance to the synthetic organic chemist.

We have found that the alkyldichlorotris(tetrahydrofuran)chromium(III) compounds **1** are likewise alkylating reagents which show high aldehyde selectivity. The reagents, which are readily accessible according to the scheme below (or from organolithium compounds)[2] were treated—partly in competition experiments—in tetrahydrofuran (THF) at −60 °C with carbonyl compounds **2**. The reaction mixture was then allowed to warm to room temperature within 18 h, and hydrolyzed with water. As shown in Table 1 the chromium compounds react with aldehydes, but not with ketones, and undergo *C*-alkylation to give the alcohols **3**[3]. Unconsumed aldehydes could not be recovered, and the ketones only to 40—71%[4].

Table 1. Aldehyde-selective alkylations with **1**.

$$R—CrCl_2(THF)_3 + R^1R^2C{=}O \rightarrow\rightarrow RR^1R^2C—OH$$
1 **2** **3**

R	R^1	R^2	1:2	3, Yield [%] [a]
CH_3	$n\text{-}C_6H_{13}$	H	3:1	85 [c]
			1:1	36 [c]
	$n\text{-}C_6H_{13}$ + C_2H_5	H + C_2H_5	2:1:1	71 [b]
				0 [b]
	CH_3	CH_3	1:1	0 [b]
$n\text{-}C_3H_7$	$n\text{-}C_6H_{13}$	H	3:1	73 [d]
			1:1	52 [b], 40 [d]
	$n\text{-}C_6H_{13}$ + C_2H_5	H + C_2H_5	2:1:1	66 [b]
				0 [b]
$n\text{-}C_4H_9$	$n\text{-}C_6H_{13}$	H	1:1	81 [e], 64 [c]
	C_2H_5	C_2H_5	1:1	0 [e]
	Ph	CH_3	1:1	0 [e]
$sec\text{-}C_4H_9$	$n\text{-}C_6H_{13}$	H	1:1	15 [e]
$n\text{-}C_8H_{17}$	$n\text{-}C_6H_{13}$	H	1:1	39 [c]
	C_2H_5	C_2H_5	1:1	0 [c]
$Ph—CH_2$	$n\text{-}C_6H_{13}$	H	3:1	65 [c]
			1:1	52 [c]
	C_2H_5	C_2H_5	1:1	0 [c]

[a] Mg- or Li-compound used for the synthesis of **1**: [b] RMgCl, [c] RMgBr, [d] RMgI, [e] RLi. Yields determined at ≥ 10 mM concentrations referred to **1**.

$$RMgHal + CrCl_3 \xrightarrow{THF} \underset{\mathbf{1}}{R—CrCl_2(THF)_3} + MgHalCl$$

In the case of acid-sensitive substrates **2** it might be advantageous to use the organochromium reagents **1**, in that they are considerably weaker Lewis acids than the above mentioned titanium reagents. As experiments with **1**, R = $n\text{-}C_3H_7$ and $n\text{-}C_4H_9$, show, the manner in which the reagent is prepared has an influence on the yield of alcohol.—The products were identified by comparison with authentic substances, and quantitatively determined by gas chromatography.

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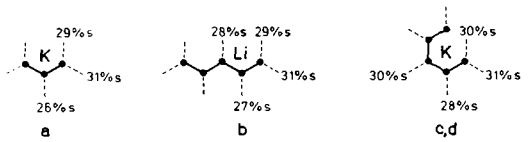
Non-Planar Structures of Allyl- and Pentadienylmetal Compounds: Pleating to Achieve a Better Charge Distribution?**

By *Manfred Schlosser** and *Manfred Stähle*

$^2J_{C,H}$ coupling constants serve as a measure of bond angles, $^3J_{H,H}$ coupling constants as a measure of dihedral angles. Taken together, both values should provide profound structural information. By this means we have reached surprising, novel conclusions on allyl- and pentadienyl-(earth) alkali metal compounds.

The C,H coupling constants at the terminal methylene groups increase uniformly along the series allylmagnesium bromide, -lithium, -sodium, and -potassium[6] and at the same time decrease at the intermediate methine groups (Table 1). Not only does the potassium compound exhibit the most striking values but also—because of frozen-in torsional movement—the *cis*- and *trans*-orientated hydrogen atoms at the allyl ends can be distinguished. All C,H bonds appear to deviate from the carbon atom plane, however, those in the *cis*- more than those in the *trans*-position. The methine group in the allyl middle even approximates a tetrahedral angle, as indicated by the "s-character" of 26% (rule of thumb[2]: $\%s = 1/5 \cdot J_{C,H}$).



In proceeding from allylpotassium **(a)** to the W-shaped[10,11] pentadienyllithium **(b)** and to the U-shaped[8,10] pentadienylpotassium **(c)**, as well as to (*E*)-hexadienylpotassium **(d)**, the s-fraction indeed increases slightly (Table 2). Despite this, the coupling constants of the *cis*-CH bonds to the electron-rich odd-numbered sites and, in particular, of the CH bonds to the even-numbered sites ("nodes") are extraordinarily small. They are hardly compatible with the assumption of completely planar structures.

The *cis*-orientated hydrogen atom at the terminus and its vicinal neighbor apparently point in opposite directions with respect to the carbon atom plane. The large H,H-coupling constants are inconsistent with any other interpretation. This gives the clue for a plausible explanation of the peculiar pleating of allyl and pentadienyl alkali metal structures. The metal atom essentially establishes a binding interaction with the electron-rich odd number sites of the ligands. In order to improve this binding, π-electron density accumulates at these positions on the metal carrying face. To compensate, the "nonbonding", even numbered sites are polarized in the opposite sense: here the higher electron density is accumulated on the metal-remote face. Because of electrostatic repulsion the CH bonds move towards the electron deficient side. The planar ideal structures **(a–d)** are deformed to give pleated structures.

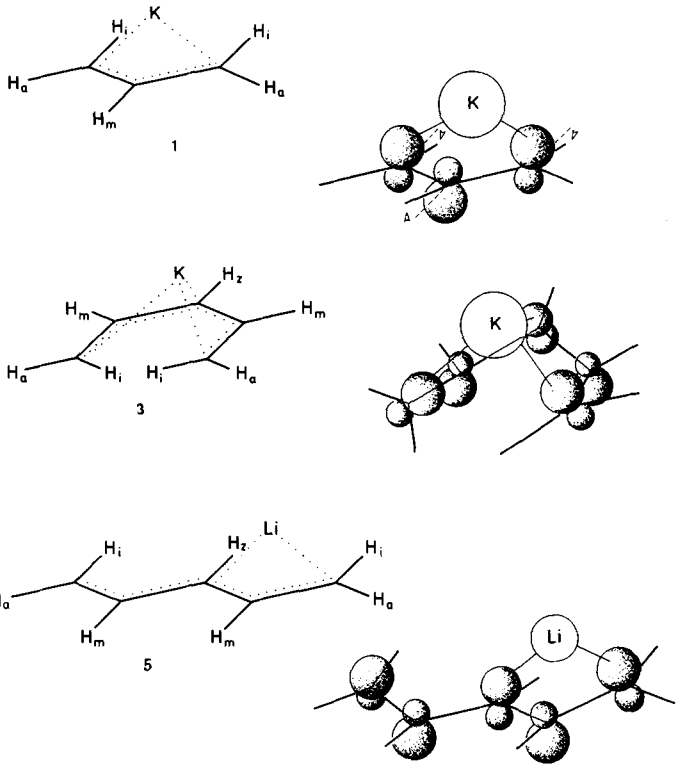


Table 1. $^{13}C,^1H$-coupling constants [Hz] of some allylmetal compounds in tetrahydrofuran (the s-character of the CH bonds is shown in parentheses). Cf. also formula **2** and details in the Supplement.

Organometallic	C,H_a	C,H_i	C,H_m
Allylmagnesium bromide	135.5 (27.1)	135.5 (27.1)	137.9 (27.6)
Allyllithium	146.5 (29.3)	146.5 (29.3)	133.0 (26.6)
Allylsodium	149.5 (29.9)	149.5 (29.9)	131.8 (26.4)
Allylpotassium	154.9 (31.0)	142.8 (28.6)	131.8 (26.4)
(*Z*)-Butenylpotassium	152.6 (30.5)	144.8 (29.0)	134.0 (26.8)
(*E*)-Butenylpotassium	153.8 (30.8)	141.6 (28.3)	128.2 (25.6)

Table 2. Chemical shifts $\delta(^{13}C)$ rel. to TMS, as well as $^{13}C,^1H$- and $^1H,^1H$-coupling constants [Hz] of some pentadienylmetal compounds in tetrahydrofuran. Cf. also formulas **3** and **5**, and details in the Supplement.

Organometallic	Conformation	δ(C-3)	δ(C-2)	δ(C-1)	C,H_a	C,H_i	C,H_m	C,H_z	H_a,H_i	H_a,H_m	H_i,H_m	H_m,H_z
Pentadienyllithium	"W"	87.3	144.0	66.0	153.8	146.5	134.2	141.6	2.7	9.0	15.3	11.6
Pentadienylpotassium	"U"	79.6	137.5	78.7	154	154	136.7	156	2.5	10.5	16.0	8.5
(*E*)-Hexadienylpotassium	"U"	74.3	136.3	75.4	150	150	143	152	2.5	10.0	15.5	8.5

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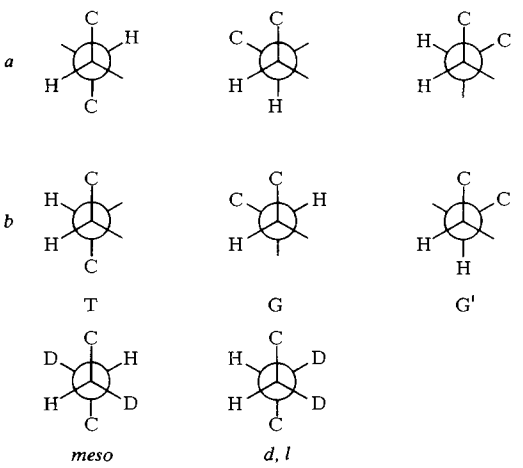
The Conformational Equilibrium of the Lower Alkanes**

By *Gerd Schrumpf**

Dedicated to Professor Oskar Glemser on the occasion of his 70th birthday

That the *trans* conformer of butane is more stable than the two *gauche* conformers has so far only been demonstrated in the gas-phase—by electron diffraction measurements[1]. We have now been able to show by NMR spectroscopy that this is also the case in solution.

The ^{1}H-NMR spectra of 1,2-disubstituted ethanes at room temperature give two coupling constants for the vicinal protons on the central C—C bond (type AA'BB' spin system[2a]) which (despite the $J_t > J_g$ rule[2b]) cannot be assigned without additional assumptions.



Scheme 1.

In the *meso*-[2,3-D_2]butane **1a**[3a] the vicinal coupling constant is clearly assigned to the proton pair *a* (Scheme 1).

CH_3–$\overset{2}{C}$HD–$\overset{3}{C}$HD–CH_3 CHD_2–$\overset{2}{C}$HD–$\overset{3}{C}$HD–CD_2–R **2**, R = CD_3
1a: *meso* **3a**, R = C_2D_5
1b: *d, l* C2–C3: *erythro* **4**, R = C_3D_7

CD_3–$\overset{2}{C}$HD–$\overset{3}{C}$HD–$\overset{4}{C}$HD–C_2H_5 **3b**, C2–C3: *threo*
C3–C4: *erythro* **3c**, C2–C3: *erythro*

The spin system of **1a** is of the $[A_3B]_2$-type[4] with numerous transitions. A precise analysis is possible only by means of the signals in the methylene region, since only here is the line density small enough to enable identification of the individual transitions. The numerical analysis of the spectrum was carried out both with lines of all subspectra as well as with those of the readily identifiable subspectrum $[D_AD_B]_2$. The results are in good agreement in both cases. A value of 8.76 Hz is obtained for the vicinal coupling constant J(2H,3H) in tetramethylsilane (TMS), *i.e.* the larger of two previously measured values[5]. This means that a larger proportion of the conformer with antiperiplanar orientation of 2-H and 3-H occurs, as observed in **1a** in the *trans*-conformation. The NMR spectrum of *d,l*-[2,3-D_2]butane **1b**[3a] in TMS was also analyzed. The vicinal coupling constant is found to be 6.11 Hz. This also is consistent with a predominance of the *trans*-conformation.

Furthermore, we have synthesized the following stereospecifically deuteriated compounds: the pentane **2**, the hexanes **3a**, **3b** and **3c**, as well as the heptane **4**. For **2**, **3a**, and **4** we obtained coupling constants J(2H,3H) of 9.13, 9.15, and 9.13 Hz, respectively. Similarly as in the case of **1a**, it can be concluded that the *trans*-conformer (C2—C3 bond) is dominant.

In the **3b/3c** mixture, the *erythro*-relationship of 3-H and 4-H is fixed by synthesis; 2-H and 3-H are oriented in the *threo*- and the *erythro*-arrangement, respectively. From the overlapping spectra we determined J(3H,4H) = 9.08 Hz and J(2H,3H) = 9.11 and 5.97 Hz, respectively. The latter finding shows that the vicinal coupling constant for the *erythro* form is here again larger than for the *threo*-form. From J(3H,4H) = 9.08 Hz it can be concluded that the conformational equilibrium is also on the side of the *trans*-conformer (C3—C4 bond)[3b] in the case of hexane in TMS.

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Selective Hydroxylations of Chiral and Substituted Paraffins**

By *Hans-Jörg Schneider* and *Walter Müller**

The selective oxidation of alkanes belongs to those accomplishments of nature, for which, so far, only very few analogous reactions can be performed in the laboratory. We wish to report that activated peroxycarboxylic acids in hydrophobic solvents convert not only cyclic[1], but also open chain hydrocarbons, such as **1**—**5**, into tertiary alcohols with high regioselectivity. With tetrahydrocitronellene **4** the configuration is retained also in the direct attack at

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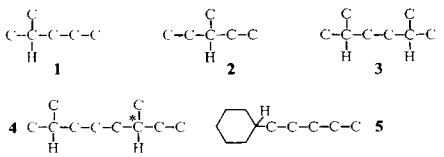
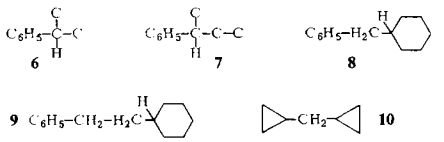
the chiral center (Table 1). Open chain hydrocarbons are generally oxidized somewhat slower than alicyclies by peroxycarboxylic acids so that radical side reactions can take place in certain circumstances.

Table 1. Hydroxylation of alkanes RH and aryl- or cyclopropyl-substituted alkanes [a].



RH	Conversion [%]	*tert*-ROH [%]	k_t/k_s [b]
1	43	77	13
2	49	84	20
3	57	93 [c]	23
4	33.5	85 [d]	23
5	15.5	77	53

After 24—48 h <4% conversion

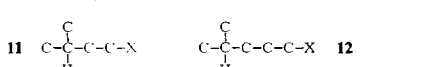


[a] In $CHCl_3$ (reflux) or at 60±5°C (**1**, **2**), RH: *p*-nitroperoxybenzoic acid 1:1 or 1:2 (**3**), 30—36 h or (**5**) [RH]=0.7—1.4 mol/L. [b] Ratio of the hydroxylation rates of *tert*- and *sec*-C—H bonds (prerequisite: attack at CH_3 < 1%). [c] 91% Mono-, 9% dihydroxy-product. [d] 38% 2-, 62% 6-hydroxy compound ($[\alpha]_D^{20} = -0.909$, ref. [4]: $[\alpha]_D^{20} = -0.78$ (neat)).

In contrast to their reactions with peroxytrifluoroacetic acid[2] substituted arenes (cf. **6**—**9**) are remarkably inert towards *p*-nitroperbenzoic acid; exeptions are only very reactive compounds such as mesitylene. Moreover, aromatic substituents even prevent attack at tertiary C—H bonds which are separated by several bonds from the π system (see compounds **8**, **9**). This is explained by the H-bond acceptor properties of arenes, which is known to reduce the reactivity of peracids in the Prileschajev reaction[3].

Similarly, oxygen substituents, which act has H-bond acceptors, lead to diminished reactivity of the substrate. This is visible in the small yields of diols obtained from alkanes where the tertiary C—H bonds are far removed from the oxygen (**3**, **4**), or with acetoxyalkanes (Table 2). With primary hydroxy or methoxy derivatives only products from the oxidation of C—H bonds in α-position to the oxygen substituent are obtained.

Table 2. Hydroxylation of heterosubstituted alkanes [a].



11, X=	H	Cl	$OOCCH_3$	OH [b]
k_X/k_H	1.00	0.06±0.01	0.06±0.02	<0.05

12, X=	H	Cl	OCH_3 [c]
k_X/k_H	1.00	0.77±0.05	<0.05

[a] Rate constants relative to **11** and **12** (X=H), from competition reactions followed by NMR analysis of the product. [b] Main products: 3-methylbutanoic acid (50%) and its ester (5%); *tert*-hydroxylation product <5%. [c] Main products: 4-methylpentanoic acid (43%), 4-methyl-1-pentanol (14%).

Polar substituents such as chlorine in **11** and **12**, which only exert inductive effects within the substrate and cannot deactivate the peroxy acids, again yield normal hydroxylation products. The reduced rate observed with γ-halogen substituents (**11**), and to a much lesser degree with δ-halogen substituents (**12**) is in accord with the electrophilic character of the reaction[1]. The observed stereospecificity, however, is at variance with carbocationic intermediates of longer lifetime.

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1 107-83-5; **2** 96-14-0; **3** 592-13-2; **4** 2051-30-1; **5** 4292-92-6; **6** 98-82-8; **7** 135-98-8; **8** 4410-75-7; **9** 1603-61-8; **10** 5685-47-2; **11** (X=H) 78-78-4; **11** (X=Cl) 107-84-6; **11** ($X=OOCCH_3$) 123-92-2; **11** (X=OH) 123-51-3; **12** (X=Cl) 62016-94-8; **12** ($X=OCH_3$) 3590-70-3; 2-methyl-2-pentanol 590-36-3; 3-methyl-3-pentanol 77-74-7; 2,5-dimethyl-2-hexanol 3730-60-7; 2,6-dimethyl-2-octanol 18479-51-7; (−)-3,1-dimethyl-3-octanol 80558-38-9; 1-(1-pentyl)cyclohexanol 30101-37-2.

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Selective Inclusion of Uncharged Guest Molecules by Neutral Hosts with Fence-Shaped Side Arms**

By *Fritz Vögtle** and *Walter M. Müller*

Dedicated to Professor Heinrich Puff on the occasion of his 60th birthday

As already observed more than 25 years ago[1], benzene and other lipophilic guest molecules appear to be intercalated in the cavities of synthetic guest molecules; however, a generalization of this type of host-guest combination[2-4] has not yet been achieved.

We have furnished multimembered monocycles with side arms, in such a way that a versatile enclosed molecular cavity for the up-take of organic guest molecules can be formed. The substituents fulfill the function of a molecular fence[6]; their number and size are determined by the number of ring members. Space filling models of compounds of this type such as **1b** show that according to this general concept, large spherically shaped molecules should be accommodated. The advantages over polycyclic large-ring cage compounds[4] are the straightforward synthesis of the monocycles and the easier adaptability to potential guest molecules caused by the conformational mobility of the framework and its arms.

For the synthesis of **1** and analogous cavity molecules **2** and **3**, *N,N'*-dibenzyl- or *N,N'*-dimethylethylenediamine were allowed to react under conditions of high dilution with the corresponding dicarboxylic acid dichlorides (terephthalic-, 4,4'-biphenyl, *o*-terphenyl-4,4''-) to give, respectively, the hexa- or tetracarboxylic acid amides, which can

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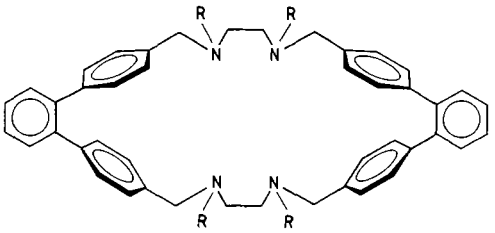
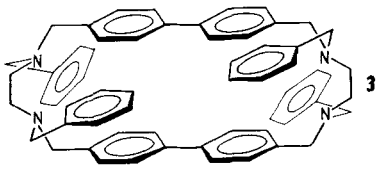
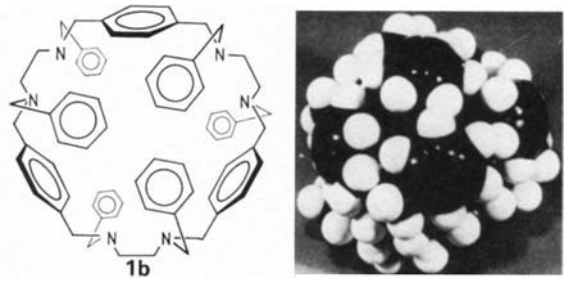




be reduced to the polyamines with B_2H_6. Apart from the trimer **1b** (20% yield, m.p. 176–178 °C), the dimers **2b** (12%, 163–165 °C), **2c** (18%, 158–162 °C), or **3** [30%, glassy, δ(benzyl-*H*) = 3.55, δ(ethano-*H*) = 2.61, in $CDCl_3$], lower and higher oligomers, which were separated chromatographically, are formed.



Whereas previous attempts to include uncharged organic guest molecules into **1b** have been unsuccessful, recrystallization of the 32-membered ring compound **2b** from *cyclohexane* produced crystals, which after drying for 24 h at 50 °C/12 torr occur as a 1 : 1 complex (93% yield, m.p. = 84–90 °C and 163–165 °C (recrystallized twice) ^{1}H-NMR, elemental analysis). Cyclohexane was tenaciously retained, as were also *dioxane*, *tetrahydropyran*, and *morpholine* even after extended drying (15 h) at 50 °C/12 torr.

In contrast, the molecules methylcyclohexane, cycloheptane, cyclooctane, decalin, and tetralin, as well as benzene and toluene, which only differ slightly in spacial requirement are not retained in a similar manner, Recrystallization of **2b** from a 1 : 1 *benzene/cyclohexane* mixture yields only the cyclohexane complex, thus opening up a separation mode for benzene and cyclohexane. Likewise, *mesitylene* adheres to a lesser extent than cyclohexane: for a few hours at 20 °C *in vacuo*; after a longer time it is removed without residue.

Although only X-ray structural analyses finally will indicate an "intramolecular" guest inclusion, or the not less interesting inclusion in the host lattice, the precise stoichiometry and selectivity of the guest up-take might indicate the first reported host-guest complexation.

Attempts at complexing with **2c**, in which the benzyl- are replaced by methyl-groups, did not lead to formation of inclusion compounds. This indicates the influence of the appropriate side arm on the host-guest interaction.

In order to investigate whether the Stetter complex[1] could be the first representative of a systematic host-guest chemistry, we studied the likewise 28-membered ring compound **3**, which also contains two biphenyl units, but in which CH_2 and N have changed places and—in the sense of our concept—substituents on nitrogen are present. This host molecule is able to stoichiometrically bind *penta-* and *hexafluorobenzene*, but not, however, benzene, cyclohexane, dioxane, and fluorobenzene.

We conclude that novel inclusion compounds between uncharged organic molecules can be tailor-made according to this principle.

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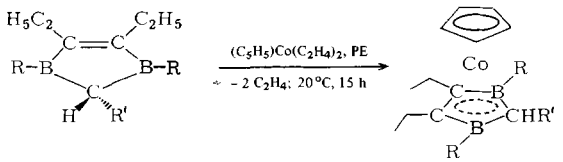
η^5-Cyclopentadienyl(η^5-1,3-diborolene)cobalt — A Novel Type of Sandwich Complexes with a Pentacoordinated Carbon Atom**

By *Walter Siebert**, *Joseph Edwin*, and *Hans Pritzkow*

During the synthesis of the paramagnetic triple-decker sandwich complex **3a**[1] from the Δ^4-1,3-diborolene **1a** and dicarbonyl(η^5-cyclopentadienyl)cobalt we found traces of the red mononuclear complex **2a**. Our hypothesis that the dinuclear complex **3** is formed by "stacking", from the sandwich **2** and a $(C_5H_5)Co$ fragment, has now been confirmed by the reaction of η^5-cyclopentadienylbis(ethene)cobalt[2] with **1b** *via* **2b** (65% yield, b.p. 70 °C/0.01 torr, m.p. 62 °C) to give the triple-decker **3b** (54% yield). **2a** can be prepared in an analogous way from **1a**[3] in petroleum ether (PE) (48% yield, m.p. 92 °C).



1a: R = C_2H_5, R' = CH_3 **2a**
1b: R = CH_3, R' = H **2b**

The constitution of these novel sandwich complexes follows from analytical and spectroscopic data: In the mass

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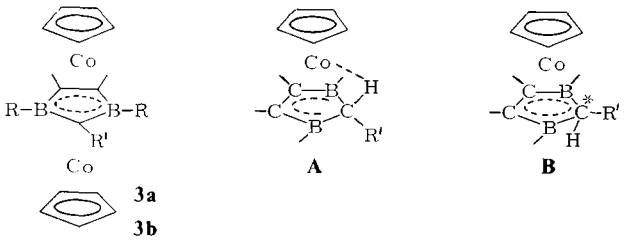
spectrum the molecular ion for **2a** appears at $m/z = 314$ (46%) and that for **2b** at $m/z = 272$ (100% rel. int.). The NMR spectra [δ¹H(C_6D_6) **2a**: 4.09 (s, 5), 2.3 (m, 2), 1.7 (m, 6), 1.35 (t, 6), 1.17 (t, 6), 0.94 (d, 3), −8.37 (q, 1); **2b**: 4.11 (s, 5), 2.3 (m, 2), 1.7 (m, 2), 1.17 (t, 6), 1.09 (s, 6), 0.11 (d, 1), −8.62 (d, 1)], with the unusual upfield shift for the proton of the CHR'-group (quartet at −8.37 and doublet at −8.62) indicate a special bonding relationship to the cobalt atom. The δ¹¹B values (27.5 and 27.3, respectively) measured for the complexes **2a** and **2b** show an upfield shift of about 41 ppm compared to the free ligands **1a** and **1b**.

On the basis of the 18-electron rule, two structures would appear possible: Structure **A** with a 3c/2e bond C—H · · · Co is consistent with the ¹H-NMR upfield shifts, as has been observed in complexes displaying C—H · · · M interaction[4]. The large $\Delta\delta$¹¹B values indicate strong metal-boron interaction, which supports a *tetra-* or *pentahapto*-structure **B** rather than that of **A**.



The X-ray structure analysis of **2a** confirms the structure **B**. Crystallographic data: orthorhombic, Pnma, $a = 9.258(3)$, $b = 15.253(4)$, $c = 12.478(3)$ Å, $V = 1762.02$ Å³, $Z = 4$; 2698 reflections, 2190 observed, $R = 0.044$, $R_w = 0.040$. The two ring ligands are coplanar, the distances of the ring planes from the cobalt atom are 1.66 [Co—(C_5H_5)] and 1.56 Å [Co—(C_2B_2C)]. In comparison to other sandwich and triple-decker complexes the diborolene ring exhibits differences at the methylene carbon atom (C*): The B—C* bonds (1.63 Å) are considerably longer, the C-atom of the methyl group ($R' = CH_3$) is shifted 0.15 Å from the best plane through the C_2B_2C-ring in the direction of the Co atom; the H atom on C* is situated on the other side of the ring, and comes into contact with the B atoms (B ····· H 1.70 Å). Despite the uncertainty regarding the position of the axial hydrogen, we interpret the spectroscopic and structural data as follows: In the sandwich complexes **2** the C atom of a methylene bridge is bound to an electron-deficient metal center (Co—C* 2.03 Å), a bonding not observed previously. The 3c/2e interaction H ····· C* ····· Co is presumably *via* an orbital with strong p-character, since $^1J_{^{13}C,H}$ is only ≈70 Hz.

Stacking onto the sandwich **2** can also be achieved with the one-electron donors (C_5H_5)Fe and $(CO)_3$Mn, whereby the corresponding 30 valence-electron triple-decker complexes are obtained from **2a** and $[(C_5H_5)Fe(CO)_2]_2$ or $Mn(CO)_{10}$ in 24 and 80% yield, respectively, *via* elimination of a hydrogen atom.

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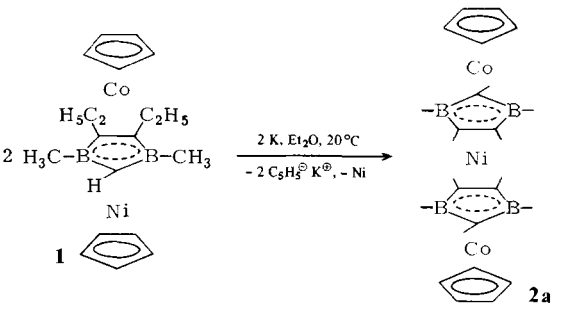
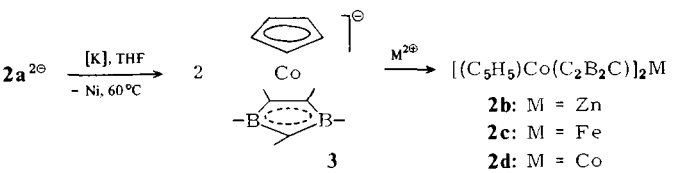
μ,η⁵-1,3-Diborolenyl Tetradecker Sandwich Complexes**

By *Walter Siebert**, *Joseph Edwin*, *Hubert Wadepohl*, and *Hans Pritzkow*

Ferrocene and cobaltocene react with alkali metal/alkene to give η⁵-cyclopentadienyl(alkene)metal complexes and cyclopentadienide[2]. Extension of this reaction to triple-decker sandwich complexes led, on reaction of paramagnetic **1** (32 valence electrons[3]) with potassium, unexpectedly to the green μ,η⁵-1,3-diborolenyl tetradecker sandwich complex **2a** (81% yield, m.p. 180 °C). From NMR and mass spectroscopic data [δ¹H(C_6D_6): −22.8, −7.0, 14.9, 18.8, 21.7; $m/z = 600$ (M^+, 100% rel. int.)] as well as chemical findings it follows that paramagnetic **2a** (44e) has a tetradecker constitution, which is confirmed by X-ray structure analysis[4]. As in the bis(μ,η⁵-1,2,5-thiadiborolene) tetradecker complexes[1] the bridging ligands in **2a** are coplanar and oriented in a *trans*-arrangement with the Ni atom as inversion center. The distances of the best ring planes to the metal atoms are 1.66 [(C_5H_5)—Co] 1.59 [Co(C_2B_2C)], and 1.75 Å [(C_2B_2C)—Ni].



The neutral complex **2a** can be reduced with potassium in tetrahydrofuran (THF) to the diamagnetic dianion $\mathbf{2a}^{2-}$ (46e) [δ¹H (D_8-THF): 0.30 (s, 6), 0.49 (s, 1), 1.33 (t, 6), 1.7 and 1.8 (m, 4), 4.03 (s, 5)], which in the presence of excess potassium slowly decomposes with elimination of Ni into two sandwich anions **3** (18e) [δ¹H(D_8-THF): 1.51 (s), 2.04 (s), 0.94 (t), 1.9 and 2.4 (m), 3.97 (s)]. On reaction with $ZnCl_2$, **3** is converted into golden-yellow **2b** [46e, isoelectronic with $\mathbf{2a}^{2-}$; 34% yield, m.p. 230 °C; δ¹H(C_6D_6): 0.91 (s, 6), 1.22 (t, 6), 2.12 (s, 1), 2.4 and 1.8 (m, 4), 4.10 (s, 5); δ¹¹B (C_6D_6): 14.0; $m/z = 606$ (M^+, 51% rel. int.)], while on reaction with $FeCl_2 \cdot 2THF$ the *paramagnetic* 42e-tetradecker **2c** [60% yield, m.p. 196 °C; $m/z = 598$ (M^+, 100% rel. int.)] is formed.



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[**] Tetradecker Complexes, Part 4. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. — Part 3: [1].

The red-brown tricobalt compound **2d** (43e) can be conveniently prepared by reaction of protonated **3** — η^5-cyclopentadienyl(η^5-1,3-diborolene)cobalt[5] — with $(C_5H_5)Co(CO)_2$ in mesitylene at 170 °C [74% yield, m.p. 209 °C; $\delta^1H(C_6D_6)$: 14.6, 9.3, −10.0, −12.9, −38.1; $m/z = 601$ (M^+, 100% rel. int.)]. Silver ions oxidize **2d** to the dark-red, diamagnetic 42e cation **2d**$^+$ [78% yield; $\delta^1H(CD_2Cl_2)$: 1.32 (s, 6), 1.27 (t, 6), 2.19 (s, 1), 2.8 and 2.1 (m, 4), 4.65 (s, 5); $\delta^{11}B$: 18.3].

These results reveal the unusual ligand properties of 1,3-diborolene for the construction of tetradecker complexes containing 42 to 46 valence electrons. With exception of the paramagnetic **2c**, with "high-spin" d^6 Fe, the new trinuclear complexes are electronically closely related to the corresponding mono- and dinuclear complexes: Formal insertion of the 12e-fragment 1,3-diborolenylcobalt [$(C_2B_2C)Co$] between C_5H_5 and Ni in nickelocene affords **1**, and then **2a**. Since the 17e-sandwich radical $[(C_5H_5)Co(C_2B_2C)]^{\odot}$ corresponds to the 5e-ligand $C_5H_5^{\odot}$, a nickelocene-like chemistry is to be expected, at least in the case of the triple-decker **1**.

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[4] Crystallographic data of **2a**: monoclinic, $P2_1/n$, $a = 8.875(2)$, $b = 15.261(7)$, $c = 10.492(4)$ Å, $\beta = 91.50(2)$, $V = 1420.6$ Å^3, $Z = 2$; 3195 unique observed reflections, $R = 0.037$, $R_w = 0.049$.
[5] W. Siebert, J. Edwin, H. Pritzkow, *Angew. Chem. 94* (1982) 147; *Angew. Chem. Int. Ed. Engl. 21* (1982) No. 2.

Isolation of Crystalline Acylsulfenyl Iodides—Intermediates in the I_2-Oxidation of Thiocarboxylic Acids

By *Shinzi Kato**, *Eiji Hattori*, *Masateru Mizuta*, and *Masaru Ishida*

Sulfenyl iodides (RSI) probably play a decisive role as reactive intermediates, both in the iodation reaction in the thyroid gland[1] and in the I_2-oxidation of thiols[2]. However, because of their instability, such compounds have rarely been investigated[3] since the first attempts were made by *Rheinboldt* and *Motzkus*[4] to isolate *tert*-butylsulfenyl iodide.

$$\underset{\mathbf{1}}{RCSHgPh} \xrightarrow{I_2} \underset{\mathbf{2}}{RCSI} + PhHgI$$

Table 1. Acylsulfenyl iodides **2** by reaction of the phenylmercury derivative **1** with iodine.

Cpd.	R	Yield [%]	M.p. [°C] [a]	IR [cm^{-1}] ν(C=O) [b]
2a	C_6H_5	72	45–46	1667
2b	4-$CH_3C_6H_4$	79	40 (dec)	1650
2c	4-$CH_3OC_6H_4$	73	32 (dec)	1648
2d	4-ClC_6H_4	64	48 (dec)	1678

[a] Decomposition. [b] KBr.

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We now report the first successful isolation of the crystalline acylsulfenyl iodides **2** (Table 1), which were obtained by reaction of phenylmercury thiocarboxylates **1** with iodine. The PhHgI, which is also formed, is readily reconverted into the educt by reaction with piperidinium- or potassium-thiocarboxylates.

The acylsulfenyl iodides **2** were characterized by spectral data and by elemental analyses. For example, in the mass spectrum, **2b** shows a molecular ion at m/z 278. The IR spectrum shows a characteristic absorption band at 1650 cm^{-1} due to the ν(C=O) vibration; its position differs distinctly from that of the corresponding band of the educt **1** (1625 cm^{-1}) and from that of bis(4-methylbenzoyl) disulfide (1692 cm^{-1}), the possible decomposition product. **2b** reacts with dithiobenzoic acid to give the unsymmetrical 4-methylbenzoyl(thiobenzoyl) disulfide[5a] in almost quantitative yield.

The acylsulfenyl iodides **2** obtained are stable for several hours at room temperature, both in the solid state and in solution (methanol or *n*-hexane); however, they decompose below 50 °C, or on irradiation with sunlight, liberating free iodine.

Experimental

2b: To a suspension of **1b**[5b] (0.21 g, 0.5 mmol) in methanol (30 ml) was added 5 mL of 0.1 N $I_2/CHCl_3$ solution. The purple colored solution immediately turned yellow. The mixture was stirred at room temperature for 1 h and then allowed to stand at *ca.* −60 °C for 1 h. After removal of the white precipitate (PhHgI) by filtration, the solvent was evaporated off *in vacuo*. Recrystallization of the solid residue from *n*-hexane (*ca.* 40 mL) at −60 °C gave 0.11 g (79%) of **2b** as a yellow microcrystalline solid.

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1a 79293-05-3; **1b** 79293-02-0; **1c** 79293-00-8; **1d** 79292-97-0; **2a** 80461-741; **2b** 80461-75-2; **2c** 80461-76-3; **2d** 80461-77-4; I_2, 7553-56-2.

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From a Formyl to a Methyl Complex

By *Heinz Berke** and *Gertrud Weiler*

Neutral formyl complexes are assumed to be important intermediates in homogeneous carbon monoxide hydrogenation processes[1]. However, their thermodynamic instability relative to the products, metal-hydride complex and carbon monoxide, has, with few exceptions[5,6], so far hindered isolation or investigation of secondary reactions. According to theoretical considerations a formyl moiety in pseudooctahedral environment should be additionally stabilized by a meridional arrangement of phosphite ligands.

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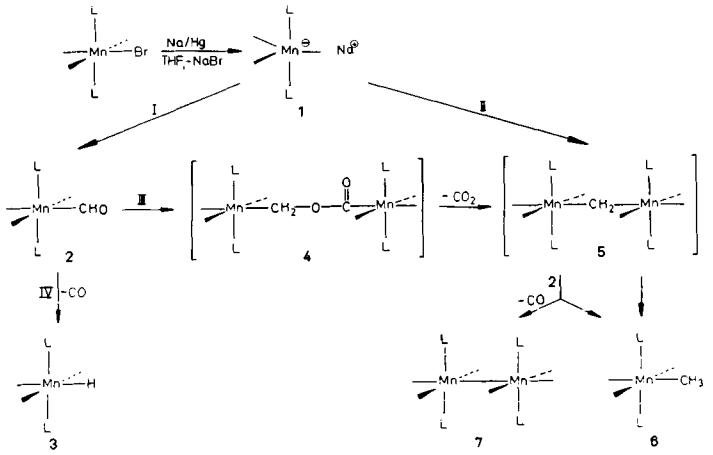
When the tricarbonylbis(trimethylphosphite)manganate(1−) ion **1** (obtained from the bromotricarbonyl complex)[11] is allowed to react with acetic formic mixed anhydride at −30 °C, the expected formylmanganese (I) compound **2** is formed.



I: −30 °C, $HCOOC(O)CH_3$; II: RT, CH_2Br_2 or $CH_2(OTos)_2$; III: 0 °C, traces of H_2O; IV: RT. L = $P(OCH_3)_3$; CO groups not shown; all reactions in tetrahydrofuran (THF).

2 was identified ^{1}H-NMR spectroscopically on the basis of its characteristic formyl resonance [(in [D$_8$]THF, rel. TMS, −30 °C): $\delta = 14.04$]. It decomposes above 0 °C, with decarbonylation to the hydrido complex **3**[12].

In the presence of catalytic amounts of water, compound **2** gives the complexes **6**[13] [m.p. 62 °C; IR (*n*-hexane): 2020, 1940, 1905 cm^{-1}; ^{1}H-NMR ([D$_6$]acetone, rel. TMS, 35 °C): $\delta = 3.73$ (t, $J = 6$ Hz), −0.3 (t, $J = 8$ Hz)] and **7** [m.p. 78 °C; IR (*n*-hexane): 2055, 1973, 1953, 1942, 1927, 1906 cm^{-1}; ^{1}H-NMR ($CDCl_3$, rel. TMS, 35 °C): $\delta = 3.87$ (t, $J = 6$ Hz); ^{31}P-NMR (toluene, rel. H_3PO_4, −30 °C): $\delta = 169.4$].

The reaction leading to **6** and **7** presumably proceeds *via* a Claisen-Tischtschenko-like disproportionation[5,6], giving the μ-methyleneoxycarbonyl complex **4**, which in turn decomposes with decarboxylation (CO_2 was identified IR spectroscopically) to the μ-methylene compound **5** [^{1}H-NMR (CS_2, rel. TMS): $\delta = 1.76$ (q, CH_2)]. We explain the formation of **7** together with **6** in terms of a hydride transfer between **2** and **5**. Moreover, **7** could possibly also be formed by decomposition of **5**.

The other feasible generation of **5** from **1** and CH_2Br_2 or CH_2(OTosyl)$_2$ and the formation of **6** from **1** (in absence of **2**) would indicate that **5** also undergoes spontaneous hydrogen disproportion. Products with carbidic bridge ligands could, however, not be detected.

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"Bichromocenylene": A Sandwich with Partly Decoupled Electrons

By *Frank Herwig Köhler*, Karl Heinz Doll, Wolfram Prössdorf*, and *Jörn Müller*

In bimetallocenylenes—alternatively: bis(fulvalene)dimetal compounds—$(C_{10}H_8)_2M_2$ (cf. Fig. 1) the ligand forces two metal atoms to a distance of >390 pm[2a]; this value raises the question of metal-metal interactions. Initial studies surprisingly indicated that $[(C_{10}H_8)_2Fe_2]^{2+}$ is diamagnetic[3], although two unpaired electrons are to be expected for a ferrocenium analogue. Later, magnetic measurements indicated that $(C_{10}H_8)_2Ni_2$ and $(C_{10}H_8)_2V_2$ are diamagnetic as well[4a]. Considering however that the MOs lie close together energetically[5], diamagnetism is not necessarily to be expected; moreover, it is still unclear by which interaction it is produced. We have synthesized the previously missing chromium compound of the $(C_{10}H_8)_2M_2$-series and found it to exhibit completely different properties. We report here on the use of NMR spectroscopy for the detection of electron interactions indicated by slight paramagnetism in coupled sandwich complexes.

We obtained bichromocenylene, $(C_{10}H_8)_2Cr_2$, **1**, as a dark powder from sodium cyclopentadienide *via* the fulvalene dianion. No contamination with possible oligomers could be detected by mass spectroscopy up to 195 °C. Referred to ^{52}Cr the most important masses at 70 eV are: $[M+2]^+$ (15), $[M+1]^+$ (44), M^+ (100), $[M-Cr-2]^+$ (15), M^{2+} (24), $C_{10}H_8^+$ (10), Cr^+ (32); the molecular ion appears with the calculated isotopic distribution. **1** is moderately soluble in toluene at 100 °C, giving a yellow solution;

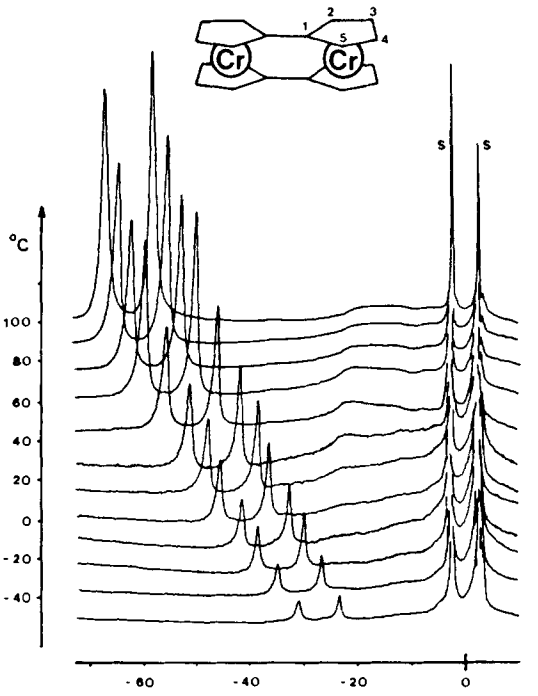

Fig. 1. 200 MHz ^{1}H-NMR spectra of $(C_{10}H_8)_2Cr_2$ **1** in [D$_8$]toluene in dependence of temperature. S = solvent. δ-Values rel. ferrocene; paramagnetic low-field shifts are negative.

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all previously reported chromocene derivatives are red. We have recorded the ^{1}H-NMR spectra (Bruker CXP 200) of a saturated solution of **1** in [D$_8$]toluene between -52 and 103 °C; besides the signals for the solvent they show only two additional signals for H2/5 and H3/4 (cf. Fig. 1).

The shifts clearly indicate that **1** is paramagnetic. However, whereas chromocene with two unpaired electrons gives δ^{para} (^{1}H) = -324 at 298K, the comparable signals of **1** are 7 times less shifted. Our findings are understandable if **1** has a diamagnetic ground state, and if paramagnetic excited states may be populated thermally. A corresponding coupling of the spins of both chromocene halves is demonstrated by the temperature dependence in Figure 1. With phenylated chromocene we could show that spin transfer to aromatic substituents is not important. Consequently, metal-metal interaction rather than superexchange dominates in the spin coupling in **1**.

Similarly as in the case of chromocene, dipolar shifts should not play a role in **1**. Thus, the temperature-dependence of the δ^{para} values may be predicted[11b]. Taking into account two excited states the fitting of the experimental data yields a singlet-triplet excitation energy which lies in the range of 300–380 cm^{-1}; the hyperfine interaction constants are 1.1 to 1.3 times greater in the second than in the first excited state. We have also observed a similar temperature behavior of paramagnetic ^{1}H-NMR signals in the case of $(C_{10}H_8)_2V_2$ and $(C_{10}H_8)_2Ni$.

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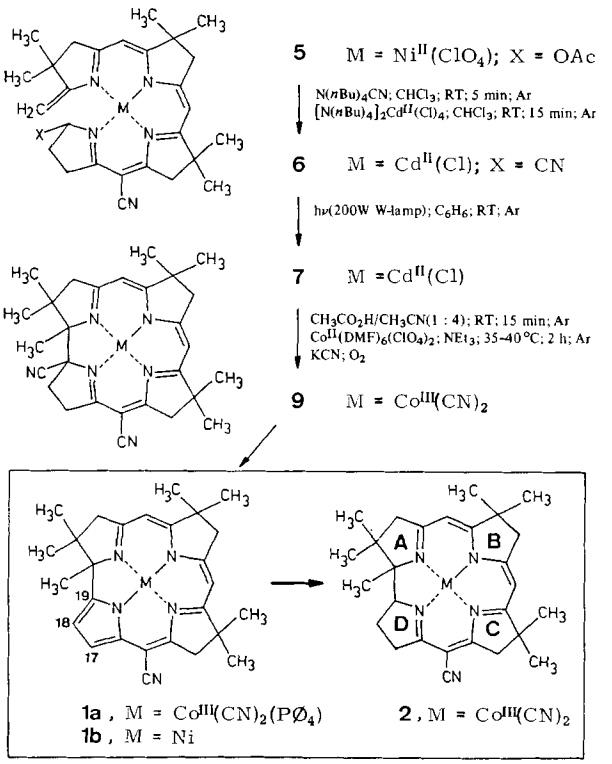
Synthesis of a Dicyanocobalt(III) D-Didehydrocorrinate and Its Reduction to the Dicyanocobalt(III) Corrinate**

By *Bernhard Kräutler* and *Kurt Hilpert**

Experimental experience regarding access to the corrin system *via* reduction of D-didehydrocorrins is still lacking, though aquisition of such knowledge is of great interest in view of the questions concerning the natural formation of corrins such as vitamin B_{12} (cf. [1]). The D-didehydrocorrin structural type became accessible for the first time in the form of the nickel(II) complex **1b** several years ago[2b, 11a,d]. For preparation of the analogous dicyanocobalt(III) D-didehydrocorrinate **1a** we made use of the electrochemically readily obtainable nickel(II) 19-acetoxysecocorrinate **5**. Outlined below is the synthetic route to the corrinoid cobalt complex **9**, the precursor of **1a**, which we obtained in *ca.* 70% overall yield. The liberation of the pyrroloid D ring of **1a** was achieved by heating a carefully degassed mixture of **9**, dimethylsulfone, and an excess of 1,8-diazabicyclo[5.4.0]undec-7-ene. The light-sensitive pyrroloid cobalt(III) D-didehydrocorrinate **1a** could be isolated in high crude yields as a green powder. The constitution of **1a** is assigned, in particular, on the basis of the ^{1}H-NMR spectrum (300 MHz, CD_2Cl_2, -40 °C). **1a** shows strongly bathochromically shifted, broad absorption bands in the UV/VIS spectrum (α-bands at *ca.* 710 nm). On shaking a benzene solution of **1a** with a 1 M aqueous HCN solution (phosphate buffer pH 3.5), **1a** can be reversibly converted into a deep-violet complex, which according to the UV/VIS spectrum (α-band at 598 nm) and ^{1}H-NMR spectrum should be the dicyanocobalt(III) Δ^{18}-didehydrocorrinate **3** formed by C-17 protonation (analogous behavior of **1b**[11d]). Treatment of **1a** with acid, without addition of HCN rapidly leads *via* **3** to a further change of color to red (loss of an axial cyano ligand (?), **3**→**4**, UV/VIS: α-band at 540 nm).



The reduction **1a**→**2** was accomplished (after treatment of **1a** with trifluoroacetic acid (→**4**)) by addition of an excess of zinc dust to an N_2-saturated acetic acid solution (RT, 1 h). Bright-red compound **2** was isolated in 22% yield by neutralization, addition of cyanide and air oxidation, and was identified after crystallization by comparison with authentic **2**[16a]. Thus, the corrin system has been shown to be accessible for the first time *via* reduction of a D-didehydrocorrin.

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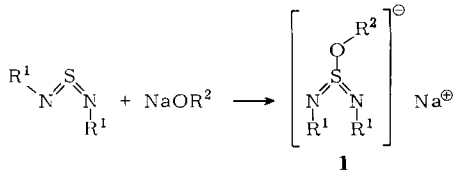
Synthesis and Structure of Triply Coordinated Sulfur Anions**

By *Herbert W. Roesky, Wilfried Schmieder, Wilhelm Isenberg, Dieter Böhler,* and *George M. Sheldrick**

No products containing triply coordinated sulfur are detected on degradation of elemental sulfur with nucleophiles in solution. In contrast, the eight-membered heterocycle $S_4N_4O_2$ reacts with sodium alkoxides to give one of the few known anions with triply coordinated sulfur[1]. We have now extended this reaction to acyclic sulfur diimides[4].



1

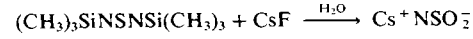
1a, $R^1 = CF_3SO_2$, $R^2 = CH_3$ } in R^2OH
1b, $R^1 = CF_3SO_2$, $R^2 = C_2H_5$ }
1c, $R^1 = C_6H_5SO_2$, $R^2 = CH_3$ } in CH_3CN
1d, $R^1 = C_6H_5SO_2$, $R^2 = C_2H_5$ }
1e, $R^1 = CH_3C_6H_4SO_2$, $R^2 = (CH_3)_2CH$ }

The very stable anions **1** thus obtained in 74—99% yield form colorless salts which are slightly sensitive to moisture and decompose at *ca.* 200 °C.

For a single crystal structure analysis, **1b** was converted into the tetraphenylphosphonium salt **1f**. The X-ray structure analysis (Fig. 1) shows that the introduction of the ethoxy group enlarges the S—N distance from *ca.* 1.53 Å to 1.609 Å (mean value).

The stability of the anions is essentially due to delocalization of the negative charge over the $—SO_2—NS(OR^2)NSO_2$-system, whereby the SO_2 groups play a cardinal role. Corresponding reactions with other sulfur diimides in which, for example, $R^1 = C_6F_5$ or $(CH_3)_3C$ proceeded in a complex manner and did not yield stable, isolable anions.

If, on the other hand, bis(trimethylsilyl)sulfur diimide **2** is allowed to react in CH_2Cl_2 with CsF, which contains about 7% water, the monomeric cesium salt **3** of the sulfonyl imide is formed:



2 **3**

Salts of the sulfonyl imide have previously only been isolated as trimers.

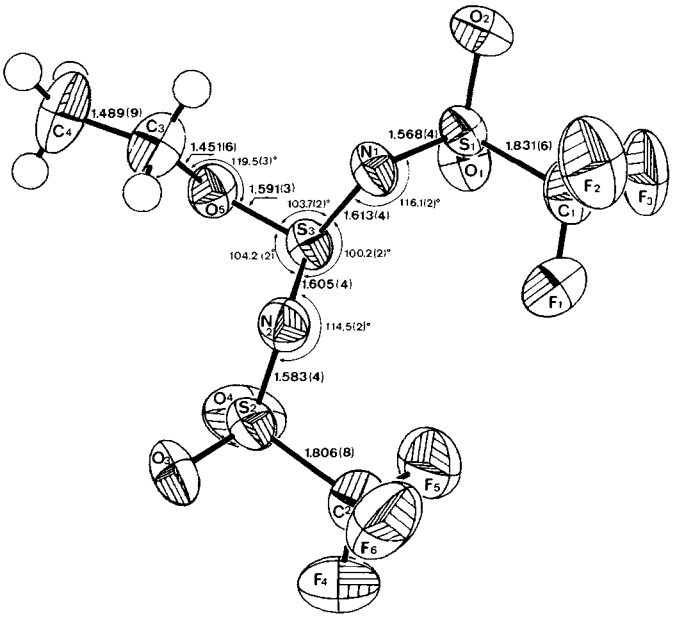


Fig. 1. Molecular structure of **1f** in the crystal; atomic distances in Å; standard deviations in brackets. S(1,2)—O(1,2,3,4) 1.423; C—F 1.313 Å; NS(1,2)O 113.1; CS(1,2)O 103.8; CS(1,2)N 102.6; OSO 118.1° (all mean values).

3, an amorphous powder that is sensitive to hydrolysis, is practically insoluble in all the usual organic solvents. For characterization of **3**, the salts $Ph_4P^+NSO_2^-$ **3a** and $Ph_3PNPPh_3^+NSO_2^-$ **3b** were prepared; in the field-desorption mass spectrum[9] they show the molecular ion. — All the new compounds have been characterized by elemental analysis and by IR, ^{1}H-NMR, and ^{19}F-NMR measurements.

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BOOK REVIEWS

The Heterocyclic Chemistry of Phosphorus. Systems Based on the Phosphorus-Carbon Bond. By *L. D. Quin.* J. Wiley & Sons, Chichester 1981.

Considering the description of the then known heterocyclic phosphorus compounds given by *F. G. Mann* in the 2nd edition of his book "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony and Bismuth" (1970), it would have been impossible for anyone to anticipate the almost explosive development of this field in hardly more than a decade since that time. This book by *Quin*, one of the most experienced and imaginative experts in the field of phospholes and their hydrogen derivatives, will become an indispensable aid to any who have to do with these compounds, though—or rather, directly because—with typical order and skill, it briefly outlines the general fundamentals required for the understanding of reactions in the

broad field of organophosphorus chemistry, for the benefit of chemists not particularly specialized in this area. The main preoccupation of the book lies in describing the syntheses and reactions of the five-ring compounds; other heterocyclic phosphorus compounds are also dealt with, though in less detail. Outstanding features of the work are an introductory chapter, in which the author has successfully tackled the task of relieving the aversion felt by many chemists for the often quite unpleasant phosphorus compounds, and three further chapters in which the spectroscopic aspects are dealt with. These latter give the most important results of ^{31}P, ^{13}C and ^{1}H-NMR spectroscopy, without which no chemist can work successfully in this field. The book concludes with a chapter on the problem of "aromaticity" in phospholes and phosphorins, and on their transition metal complexes—though the latter are treated somewhat briefly. Thanks to the many references given, the book is also an indispensable aid to the specialist. The present high rate of development will no doubt very soon necessitate a second edition, in which the few and mostly quite trivial printing errors in the text and formulas can be corrected. All in all, this is a long-awaited book, of appeal not only to the "phosphorus chemist" but also to any who desire a brief review of the state of knowledge in organophosphorus chemistry, and not just the heterocyclic compounds.

Karl Dimroth [NB 556 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 (Federal Republic of Germany).

Concepts in Drug Metabolism. Part B. Edited by *P. Jenner* and *B. Testa*. Marcel Dekker, Basel 1981. x, 627 pp., bound, SFr 185.00.—ISBN 0-8247-1323-0

The Alkaloids. Vol. 18. Edited by *R. H. F. Manske* and *R. G. A. Rodrigo*. Academic Press, New York 1981. xvi, 411 pp., bound, $ 65.00.—ISBN 0-12-469518-3

Applications of Glass Capillary Gas Chromatography. Edited by *W. G. Jennings*. Marcel Dekker, Basel 1981. viii, 629 pp., bound, SFr 186.00.—ISBN 0-8247-1223-4

Gmelin Handbuch der Anorganischen Chemie. Springer-Verlag, Berlin 1981. 8th Edit.

Sc, Y, La-Lu - Seltenerdelemente. Teil A: Geschichtliches. Vorkommen. Lieferung 5: Y, La und Lanthanide. Geochemie: Gesamterde. Magnetische Abfolge. xxiv, 475 pp., bound, DM 1287.00.—ISBN 3-540-93439-1

Mn - Manganese. Part C7: Compounds of Manganese with Boron and Carbon. xv, 248 pp., bound, DM 677.00.—ISBN 3-540-93438-3

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Ac - Actinium Supplement Bd. 1. xvi, 316 pp., bound, DM 881.00.—ISBN 3-540-93445-6

B - Boron Supplement Bd. 2: Elemental Boron. Boron Carbides. xvi, 242 pp., bound, DM 678.00.—ISBN 3-540-93448-0

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Steroid Analysis by HPLC. Vol. 16. Edited by *M. P. Kautsky*. Marcel Dekker, Basel 1981. xii, 397 pp., bound, SFr 135.00.—ISBN 0-8247-1324-9

The Chemistry of Chalcones and Related Compounds. By *D. Nath Dhar*. John Wiley & Sons, Chichester 1981. xiii, 285 pp., bound, £ 28.50.—ISBN 0-471-08007-1

Matrix Isolation Spectroscopy. Edited by *A. J. Barnes, W. J. Orville-Thomas, A. Müller,* and *R. Gaufrès*. D. Reidel Publishing Company, Dordrecht 1981. x, 605 pp., bound, Dfl 160.00.—ISBN 90-277-1328-6

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Advances in Selective Chemical Syntheses of Complex Oligosaccharides

By Hans Paulsen*

A wide variety of complex oligosaccharides has now been made accessible as a result of methodological improvements in the sphere of chemical synthesis, which can be used for the study of conformations and interactions with protein-receptor molecules. Such work is of particular importance because the oligosaccharide chains of glycoproteins and glycolipids anchored to the plasma membrane are important in cell-cell interactions and are receptors for enzymes, hormones, proteins, and viruses; furthermore, they determine the antigen properties of cells. The methods of synthesis available for the production of selective linkages in oligosaccharides are dealt with, particular attention being paid to conversion of saccharides into oligosaccharides, which are important from the biological point of view.

1. Introduction

Carbohydrate chemistry, and especially the sector of monosaccharides, is currently undergoing a major upsurge that started in the mid-1950's following the introduction of new synthetic methods, analytical methods of separation, and the appearance of new possibilities of elucidating structures by physicochemical methods. Many new natural sugars were discovered as a result, and a particularly stimulating factor was the discovery of some unusual amino sugars in aminoglycoside antibiotics and bacterial polysaccharides[1]. The development of stereo- and enantioselective syntheses made it possible to synthesize virtually any desired sugar and amino sugar starting from various readily accessible saccharides. Interest in asymmetric syntheses was already growing in organic chemistry at that time, and it also became possible to extend the modification techniques to complex aminoglycoside antibiotics to obtain modified products[2].

Some decisive developments occurred at the beginning of the 1970's. By his discovery of sugar-nucleotide compounds, which led to the clarification of the biosynthesis of polysaccharides, *Leloir*[3] pushed carbohydrates once again into the center of the biochemical arena. Whereas hitherto polysaccharides had been regarded only as a supporting material and a source of energy, the importance of the complex glycoconjugates was now recognized[4–6]. These compounds, difficult to investigate, contain a protein, lipid, or phospholipid component in addition to an oligosaccharide chain. It was found that it was the oligosaccharide residue of the glycoconjugates that is of importance for the biological functions of this class of substances. There therefore followed a tumultuous development in glycoconjugate biochemistry.

The glycoconjugates include, for example, glycolipids, whose lipid part serves as a means of anchorage in the double layer of the cell membrane[7]: the oligosaccharide component protrudes from the cell membrane and is the determinant whose structure is decisive for the specificity of the immune reaction[8]. The glycoproteins found on the cell-surface membranes, in which the oligosaccharide residue is likewise exposed, play a role in intercellular recog-

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nition[9, 10], acting as receptors for enzymes, hormones, proteins, and viruses. They are able to regulate the transportation of proteins between cells, and should thus be regarded as signal substances in cell metabolism[4, 10]. Glycoproteins are also important in governing the water-molecule concentration at the membrane and the permeation of inorganic ions. In addition, they protect the peptide chain against proteolytic attack. Intensive studies are in progress for the purpose of a more detailed clarification of these many functions. The prophetic words of *Nathan Sharon* indeed seem to have come true—"We know now that the specificity of many natural polymers is written in terms of sugar residues, not of amino acids or nucleotides"[4a].

The advances made in this sphere have been due to the improvements made in recent years in the chemical, physical, and enzymic methods of structure analysis[10]. High-field NMR spectroscopy, in particular, has contributed to rapid clarification of the structure of the oligosaccharide chains in glycoproteins. The sequence in the oligosaccharide residue is now known in an appreciable number of glycoproteins and glycolipids, and it is also known that it is largely the terminal sequences of the oligosaccharide, the determinants or antennae, that are responsible for the specific biological action. Preparative organic chemists are now called upon to synthesize such sequences of oligosaccharide determinants since biogenic material is frequently difficult to obtain. Modified determinants could provide information on the nature of the sites of attachment and thus on the mechanism of the biological interaction between the oligosaccharide hapten and the antibody or protein with which it reacts. The aim of this review is to report the advances made in the field of selective chemical synthesis of oligosaccharides.

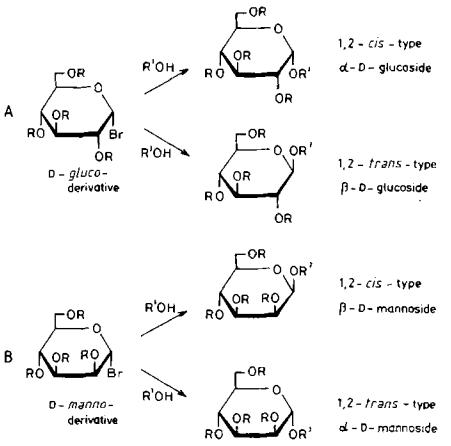
2. Selective Oligosaccharide Synthesis

2.1. General Points

Until a few years ago the synthesis of a disaccharide was still an outstanding achievement, and syntheses of trisaccharides with various structural units and types of linkages were successful only in isolated cases[11, 12]. Although we have now learned to synthesize oligosaccharides, it should be emphasized that each oligosaccharide synthesis remains an independent problem, whose resolution requires considerable systematic research and a good deal of know-how. There are no universal reaction conditions for oligosaccharide syntheses.

In an oligosaccharide synthesis two polyfunctional reaction partners must be coupled. Both must be able to be selectively blocked and deblocked. In the glycosyl component it must be possible to expose and functionalize the anomeric center: in the hydroxyl component only the hydroxyl group intended for the coupling step must be selectively deblocked. The reactivities at the anomeric center of the glycosyl component and of the OH group of the reaction partner depend very strongly on the type of blocking pattern of the two compounds. A variation of the blocking pattern can exert a decisive influence on the coupling step. Conformational and steric influences, and the molecular sizes of the two partners are also significant. The coupling step should proceed as stereoselectively as possible and result in only one of the two possible anomers if expensive anomer separation is to be avoided, a procedure that is extremely difficult in the case of the larger oligosaccharides. All these relationships mean that the reaction conditions must be carefully tried out for each coupling step, and solid-state oligosaccharide syntheses, such as are used successfully for peptides and nucleotides, therefore do not seem very promising. Experiments performed in this direction have not yielded any useful procedures[13].

In the syntheses of the larger oligosaccharides, glycosyl halides are still the most important educts, whose reactivity can be modified over wide limits *via* blocking groups; many suitable catalysts can be selected according to each purpose. A number of different glycoside-linking methods have also been investigated, but so far these have been used only occasionally for the synthesis of large molecules.



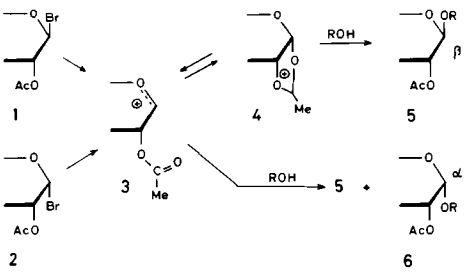
Since the methods for coupling two sugar residues with formation of a 1,2-*cis*- or 1,2-*trans*-glycopyranoside bond are completely different, the two types of reaction will be treated separately. In the case of the 1,2-*cis* type **A** the establishment of an α-glycoside link in the *gluco*- and *galacto*-series is involved, and the production of a β-glycoside bond in the *manno* series. Correspondingly, formation of a 1,2-*trans*-type **B** involves the production of a β-glycoside bond in the *gluco*- and *galacto*-series and of an α-glycoside bond in the *manno*-series. Thereby the essential structures occurring in biologically important oligosaccharides are covered.

2.2. Preparation of 1,2-*cis*-Glycopyranoside Bonds

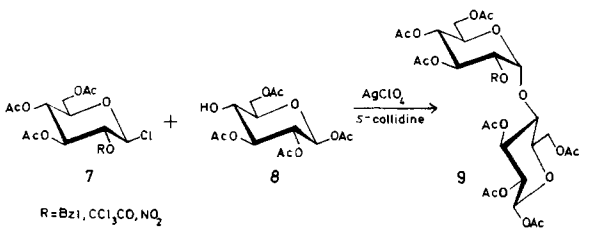
2.2.1. α-Glycopyranosides of the *gluco*- and *galacto*-Series

After the halide has been split off, pyranosyl halides in which the H atom on 2-OH is replaced by a neighboring-group-active substituent, irrespective of whether the β-form **1** or the α-form **2** is used, react *via* the oxocarbenium ion **3** to give the dioxocarbenium ion (acetoxonium ion) **4**, which is stabilized with respect to the more reactive **3**[14]. Nucleophilic ring opening of **4** with an alcohol component at C-1 leads, for steric reasons, only to the β-glycoside **5**.

This reaction sequence is utilized to bring about stereoselective β-glycoside synthesis (Section 2.3). In reactions with only moderately reactive alcohols, **3** is also sometimes capable of reacting, so that an anomeric mixture of **5** and **6** forms.



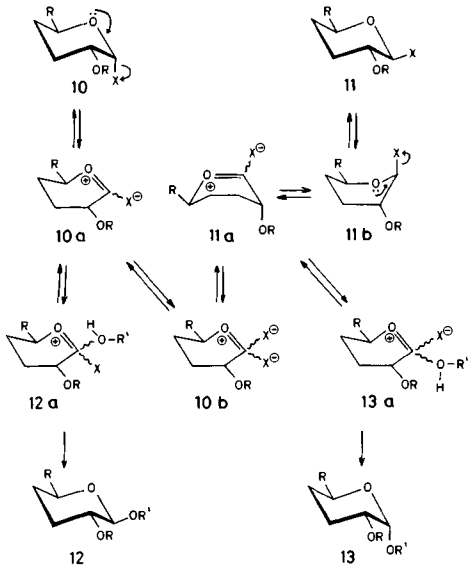
The first prerequisite for an α-glycoside synthesis is thus that the H atom of 2-OH of the pyranosyl halide must have been replaced by a nonneighboring-group-active substituent. As shown in reactions **7**→**9**, a number of substituents have been tried out for this purpose[*]. The benzyl group has proved the most favorable, since good reactivity of the halide is observed. In the case of the likewise well tried trichloroacetyl group the halide is more stable but its reactivity is lower.



To achieve an α-glycoside synthesis the less stable β-halide **7** must be taken as the starting substance and the nucleophilic substitution with the alcohol component be conducted in such a way that it proceeds as completely as possible with inversion in the sense of an S_N2 reaction. This can be done in a solvent of low polarity such as dichloromethane or ether in the presence of an active catalyst such as $AgClO_4$ or $AgClO_4/Ag_2CO_3$. Thus, **7** (R = Bzl) reacts with the extremely weakly reactive 4-OH group of **8** to give the maltose derivative **9** (43%)[15]. Corresponding reactions can be carried out with **7** ($R = CCl_3CO$)[16].

However, this process is possible only with relatively stable isolable β-halides. In the majority of cases the labile β-halide can be used only with difficulty, or indeed not at all. This applies in particular to the disaccharide halides, intended for the construction of larger units. In this respect the process has only limited applicability.

Synthesis of α-glycosides by in situ anomerization of α-glycosyl halides: To avoid these difficulties, the α-glycoside synthesis must proceed directly from the more easily accessible and more stable α-glycosyl halide **10.** According to *Lemieux et al.*[17], the α-halogenide **10** exists in equilibrium with the more unstable β-halide **11**; the equilibration reaction is catalyzed by halide ions. Especially when a solvent of low polarity is used, such as dichloromethane, one ion pair **10a** can be produced from the α-halide **10,** and a different ion pair **11a** from the β-halide **11** *via* conformation **11b.** The two ion pairs **10a** and **11a** are in equilibrium *via* the ion triplet **10b**[18]. At equilibrium the proportion of more stable **10** is high. Destabilization of the β-halide **11** takes place as a result of an anomeric effect, which is particularly powerful in halide substituents.



The energy barrier for a nucleophilic reaction of glycosyl halides such as **10** and **11** with alcohols R'OH with inversion *via* **11**→**11a**→**13a**→**13** is lower than that for the corresponding reaction **10**→**10a**→**12a**→**12,** so that formation of α-glycoside **13** is faster than that of β-glycoside **12**[18]. Control of the whole reaction, exploiting this difference in reaction rates, permits the selective synthesis of α-glycosides from the α-halide **10.** If this difference is large enough, it is possible to steer the whole reaction so that virtually no β-glycoside is produced, and the only product is the α-glycoside **13,** even if the concentration of **11** or **11a** is low. However, the establishment of the equilibrium **10** ⇌ **11** must be fast enough so that new **11** or **11a** can be constantly produced from **10.**

In this reaction, termed a halide-catalyzed glycosidation by *Lemieux et al.*[18] tetraalkylammonium halides were used as catalysts. The reaction has proved itself in many instances, but requires very reactive pyranosyl halides and relatively long reaction times. The high selectivity indicates a reaction sequence proceeding *via* the extremely reactive β-halide-like ion pair **11a.** The preferential formation of α-glycoside cannot be attributed to an anomeric effect. If a polar solvent is used for the reaction, separated ion pairs with carboxonium-like intermediate cations occur, and the selectivity is considerably reduced. Anomeric mixtures are also obtained in the subsequent isomerization of the glycosides.

Reaction of the α-halide **10** to the α-glycoside **13** in dichloromethane can also be carried out in presence of the

[*] In accordance with the rules of the International Union of Biochemistry the following abbreviations have been used: Ac = acetyl, Bz = benzoyl, Bzl = benzyl, Cbz = benzoyloxycarbonyl, Trt = trityl. Other abbreviations are explained in the text.

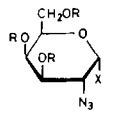
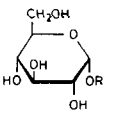
soluble catalysts mercuric cyanide, mercuric bromide, silver perchlorate, and silver triflate likewise with high selectivity[19]. These catalysts are actually much more active than tetraethylammonium halides, and, even less reactive halides react under very much milder conditions[19-21]. We presume that the α-halide complexes with the mercury salts, and probably also with the silver salts, to form ion pairs **10a, 10b,** and **11a** whose precise structures are, however, unknown (X would then be $BrHgBr_2$, $BrHg(CN)_2$, or ClO_4 or CF_3SO_3).

The energy barrier for the reaction sequence **11a**→**13a**→**13,** as well as that for **10a**→**12a**→**12** may be lowered, so that over-all both reactions are accelerated. It should be borne in mind that if the catalysis is too strong, the difference between the rates of formation of **13** and **12** can decrease, with an adverse effect on selectivity. Even if it is assumed that in the reaction of the α-halide **10** with $AgClO_4$ or $AgCF_3SO_3$ only glycosyl perchlorates[14] or glycosyl triflates are formed, the preferred formation of **13** (X = ClO_4 or CF_3SO_3) can be analogously explained[20,21].

The course of an oligosaccharide synthesis can be essentially influenced by the reactivities of the halide, the catalyst, and the alcohol[21]. The reactions are conducted in solvents of low polarity, such as dichloromethane, possibly mixed with toluene.

The reactivity of the halide is influenced primarily by varying the substituents on the hydroxyl groups (see Table 1). Benzyl compounds are always more reactive than the acetylated or benzoylated derivatives, the position of the benzyl ether groups being less important than their number. This is apparent in the rates of anomerization of α-glycosyl halides carrying mixed substituents and in comparable reactions[22]. Trichloroacetyl groups decrease, and deoxy groups increase the reactivity of the halide, the effect being large in both cases. Bromides are always more reactive than chlorides, but they are also less stable.

Table 1. Reactivity of halides, catalysts, and alcohols in oligosaccharide synthesis.

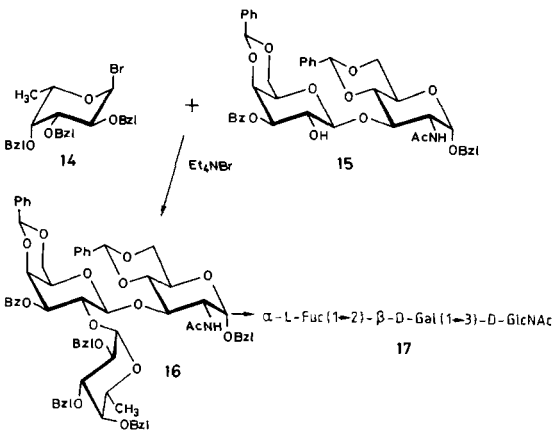
Halide	Catalyst	Alcohol
 R ~ Bzl > Bz ≳ Ac; X ~ I > Br > Cl	Et_4NBr / molecular sieve 4 Å $Hg(CN)_2$ $Hg(CN)_2$ / $HgBr_2$ $HgBr_2$ / molecular sieve 4 Å $AgClO_4$, Ag_2CO_3 Ag triflate, Ag_2CO_3	HO-CH_3 >> HO-CH_2R > 6-OH  6-OH >> 3-OH > 2-OH > 4-OH

The catalyst must be regarded as the most important factor influencing the reaction. A tetraethylammonium halide is the mildest catalyst and demands very high reactivity on the part of the two reactants. If the reaction is carried out with the very mild catalyst tetraethylammonium chloride, in accordance with the original procedure[18], the solvent is dichloromethane with a small amount of dimethylformamide. Mercury compounds are more catalytically active and can also be used as mixtures in various proportions (see Table 1). Most active of all are silver perchlorate and silver triflate. In the case of the triflate it should be borne in mind that the reaction of α-halide to β-glycoside is also catalyzed, so that the stereoselectivity can decrease; this can be countered by conducting the reaction at a lower temperature.

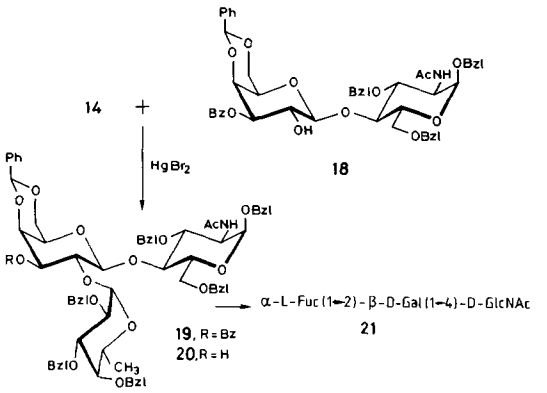
As a rule the reactivity of the alcohol cannot really be influenced, since as a reaction partner it is determined in advance. On the whole, it can also be said that alkyl substituted derivatives are more reactive than those bearing acyl substituents[23]. Secondary hydroxyl groups in pyranoses, which are important for saccharide linkages, have a moderate reactivity and are particularly suitable for reactions with reactive halides under the above conditions, whereby a high selectivity is achieved. Primary hydroxyl groups such as the 6-OH of sugars or that in serine are considerably more reactive. In this case the differences in the rates of reactions to α- and β-glycoside are smaller, and the stereoselectivity decreases. In such instances a milder catalyst must be selected or, as described above, the pure β-halide must be used directly. The β-halide can also be obtained by controlled inversion techniques[24-26], whereby it must be used directly for the reaction. The most reactive hydroxyl group is found in methanol whose reactions are therefore least comparable with those of saccharides.

In all glycoside syntheses it is extremely important to make absolutely certain that moisture is excluded, and all operations should be carried out under argon or nitrogen using the same techniques employed for sensitive organometallic compounds. Traces of moisture frequently result in considerable losses in yield and are the usual cause of failure to achieve the desired result; it is also recommended that reactions be performed in brown glass vessels.

Influence of the catalyst reactivity: The *in situ* anomerization method can be applied very advantageously to the halide of L-fucose **14.** In the presence of the mild catalyst tetraethylammonium bromide, **14** reacts with the disaccharide **15** to give the trisaccharide **16,** this reaction being stereoselective with a yield of 80% relative to the α-glycoside **16**[27]. Deblocking of **16** yields **17,** the trisaccharide determinant of blood-group substance H (type 1). α-L-Fuc(1→2)-[α-D-Gal(1→3)]-D-Gal, the trisaccharide determinant of blood-group substance B (type 1)[28], and β-D-Gal(1→3)-[α-L-Fuc(1→4)]-D-GlcNAc, the trisaccharide determinant of the Lewis a blood-group substance[29,30] have been analogously produced.

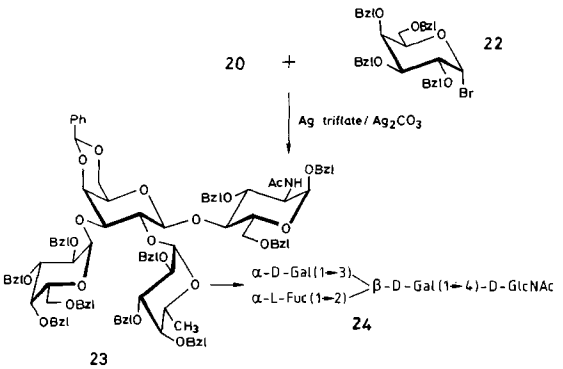


In the very similar disaccharide **18,** surprisingly enough, the 2-OH group of the non-reducing unit is considerably less reactive than that of disaccharide **15.** Disaccharides **15** and **18** are identical in the non-reducing unit and differ only in the type of linkage: in **15** a 1→3-, while in **18** a 1→4-link is present. In the presence of tetraethylammonium chloride catalyst **18** reacts with fucosyl bromide **14** to give the trisaccharide **19** in only 30% yield. The reaction can now be improved by increasing the reactivity of the catalyst. Thus, 40, 50, and 80% yields of **19** can be obtained with $Hg(CN)_2$, $Hg(CN)_2/HgBr_2$, $HgBr_2$ catalysts, respectively, the reaction proceeding stereoselectively so that only the α-glycoside is produced[21]. The determinant of blood-group substance H (type 2) **21** can be obtained from **19**[21,31].



With L-fucose derivatives the situation is so favorable that the selectivity hardly decreases in the *in situ* anomerization reaction, even in the polar medium nitromethane/toluene—in contrast to D-galactose and D-glucose derivatives. In the presence of $Hg(CN)_2$ in nitromethane/toluene, the disaccharides α-L-Fuc(1→3)-L-Fuc[32], α-L-Fuc(1→4)-L-Fuc[33], and α-L-Fuc(1→2)-L-Fuc[34] can be obtained with good selectivity. The determinants of the Lewis d blood-group substance, in which two L-fucose residues are connected in a stepwise manner to β-D-Gal(1→4)-D-GlcNAc, were synthesized by tetraethylammonium halide catalysis in 1,2-dichloroethane[35].

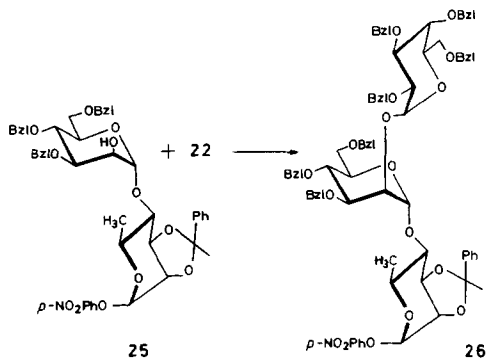
Likewise, α-glycoside linkages can be produced stereoselectively with the pyranosyl halide of D-galactose **22** and the corresponding D-glucose compound by *in situ* anomerization in the presence of tetraethylammonium halide. This is demonstrated in the above-mentioned synthesis of the trisaccharide determinant of blood-group substance B[28]



and in the synthesis of the unit α-D-Glu(1→2)-D-Gal[36,37].

In the more difficult oligosaccharide syntheses the hydroxyl groups are often less reactive, and a far more reactive catalyst is needed than tetraethylammonium chloride. When the trisaccharide **20** reacts with the galactopyranosyl bromide **22** in the presence of tetraethylammonium chloride, practically no coupled product **23** is formed; an 80% yield of pure α-linked tetrasaccharide **23** is, however, produced with $HgBr_2$, and a molecular sieve of 4 Å, and a 77% yield of **23** is obtained with silver triflate/silver carbonate[27]. It should be noted that the reaction with triflate must be performed at −25 °C to preserve the stereoselectivity. In selecting the catalyst a compromise must be reached between yield and selectivity. The tetrasaccharide **23** can be deblocked to **24,** the tetrasaccharide determinant of blood-group substance B (type 2)[27].

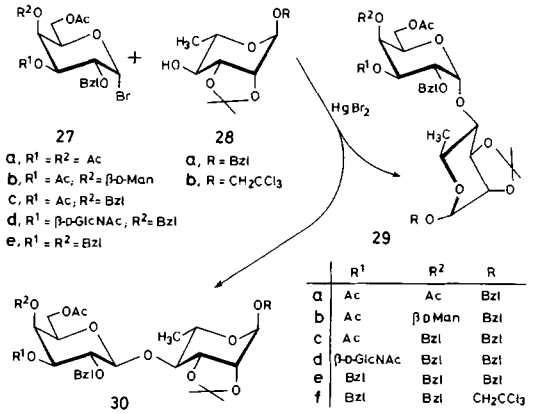
The trisaccharide **26** is obtained with good stereoselectivity from the galactose derivative **22** and the disaccharide **25**[38]. Deblocking **26** gives α-D-Gal(1→2)-α-D-Man(1→4)-α-L-Rha, which represents the repeating unit of a *Salmonella* lipopolysaccharide. Silver triflate/s-collidine in toluene at −70 to 20 °C is used as the catalyst.



It may be emphasized that in the reaction with galactopyranosyl bromide **22** the selectivity decreases if a polar solvent such as nitromethane/benzene is used in place of dichloromethane or toluene. As has been demonstrated[39,40], although the α-glycoside-linked compound is obtained as the main product, the proportion of a β-glycoside product is still considerable.

The influence exerted by the reactivity of the halide and the hydroxyl component was studied using a model reaction between variously substituted galactosyl bromides **27** and the rhamnosides **28a** and **28b**[41]. The reactions were carried out under standardized conditions ($HgBr_2/CH_2Cl_2$) and the selectivity determined. The 4-OH group of the rhamnose derivative **28** is almost as reactive as that of a primary 6-OH group. In components with reactive hydroxyl groups the selectivity can be considerably impaired during glycoside synthesis, since reactions **10**→**13** are partially replaced by reactions **10**→**12.** It is then necessary to improve the selectivity either by reducing the reactivity of the halide or through a milder catalyst.

The bromides **27a** to **27e** vary considerably in reactivity (see Table 1); benzyl groups increase, and acetyl groups decrease reactivity. An additional glycosyl residue has only a slightly weaker activating effect than a benzyl group.



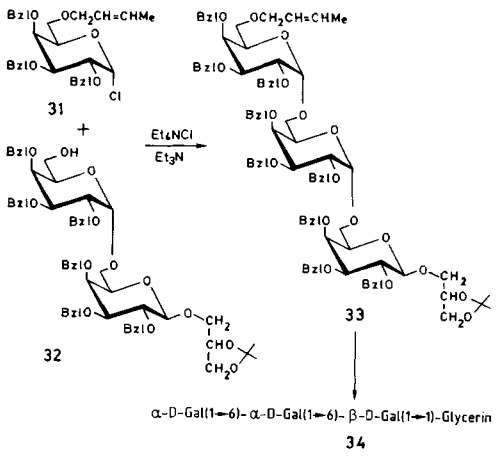
The least reactive bromide **27a** reacted with **28a** to always give the α-linked disaccharide **29a.** The most reactive bromide **27e,** on the other hand, gives a mixture of anomers **29e** and **30e** (19:81) with **28a** *i.e.* the β-form is therefore now the main product. The compounds with mixed substitution **27b** to **27d** have intermediate reactivity. Thus reaction of the disaccharide halide **27b** with **28a** yields virtually only the α-linked trisaccharide **29b.** The corresponding reaction of the mixed-substituted compound **27c,** on the other hand, yields an α:β product ratio [**29c** : **30c**] of (88:12), and **27d** gives a product mixture with an α:β ratio [**29d** : **30d**] of 16:84. These examples clearly show how the selectivity can be influenced by the reactivity of the halide used[41].

The reactivity of the hydroxyl group in the rhamnoside **28a** was reduced by exchange of the benzyl for a trichloroethyl group, and reacted with the most reactive halide **27e** under standard conditions to give the anomeric mixture **29f/30f** (81:19). The product ratio has therefore now been shifted in favor of the α-form, in contrast to the reaction of **27e** with **28a.** A similar effect can be observed in other glycosidation reactions with **28b.** It is therefore possible to modify the reactivity of the hydroxyl component by varying its substituents, and thus to influence the selectivity of the reaction[41].

Of course the catalyst can be varied to improve the poor selectivity of the reaction of **27e** with **28a.** If instead of $HgBr_2$ the milder catalyst tetraethylammonium bromide is used, the reaction of **27e** with **28a** yields almost exclusively the α-glycoside **29e,** although reduction in yield can occur[20]. With sensitive disaccharide and trisaccharide halides the halide-catalyzed reaction cannot be carried out with tetraethylammonium halide, since too much time and an elevated temperatures are required. Disaccharide and trisaccharide halides must be treated as quickly as possible with the most reactive catalysts.

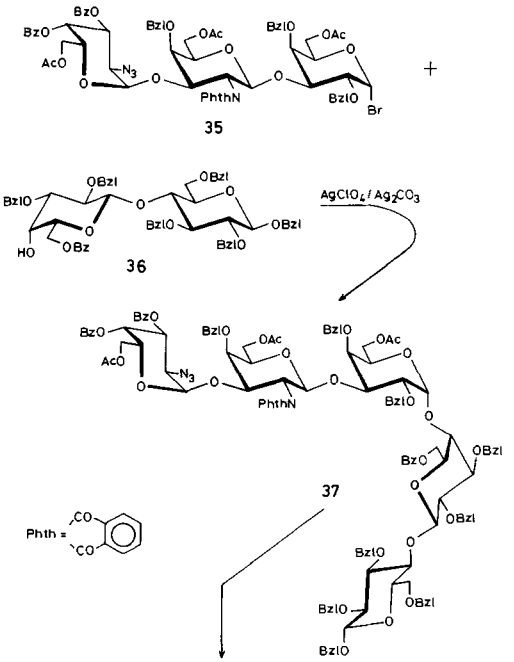
The fact that very reactive 6-OH groups can be converted into α-glycosides with satisfactory selectivity is demonstrated by the synthesis of α-D-Glc(1→6)-D-Gal and α-D-Gal(1→6)-D-Gal[42,43]. In these instances a mild tetraethylammonium halide catalyst was used to afford good selectivity. Under these reaction conditions the halide **31** reacts with the disaccharide **32** to give a trisaccharide glyceride **33,** which could be deblocked to give **34.**

Summarizing, it can be said[21,41] that reactive halides can react with hydroxyl groups of moderate reactivity to give α-glycosides in very high selectivity. The catalyst should be selected to suit the reactivity of the hydroxyl group. In the case of very reactive hydroxyl groups the reactivity of the halide or the catalyst must be reduced to



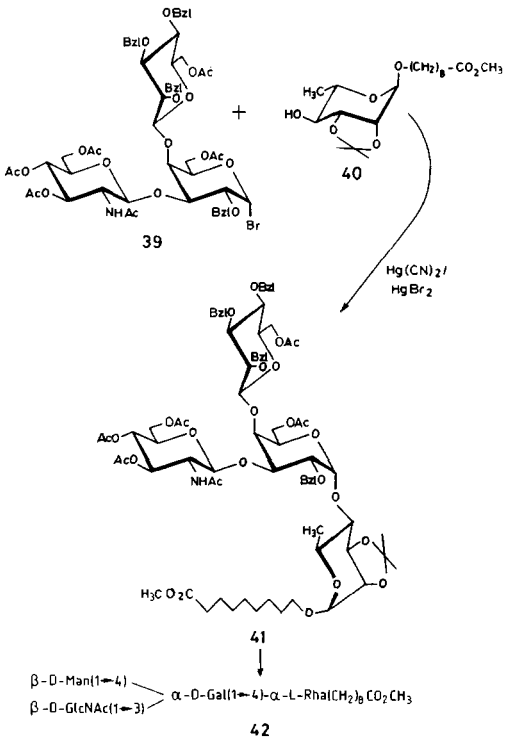
maintain satisfactory selectivity as regards the anomeric ratio, or the pure β-halide must be used as the starting material.

Block Syntheses: Since as a result of *in situ* anomerization a very reactive β-halide-like intermediate reacts to give an α-glycoside stabilized by the anomeric effect, this coupling method can be regarded as extremely effective. It is also suitable for coupling previously prepared oligosaccharide units to larger molecules, potentially a very useful way of making larger complex oligosaccharides. In the synthesis of longer saccharide chains it is therefore advantageous to select an α-glycosidic linkage for the block cou-



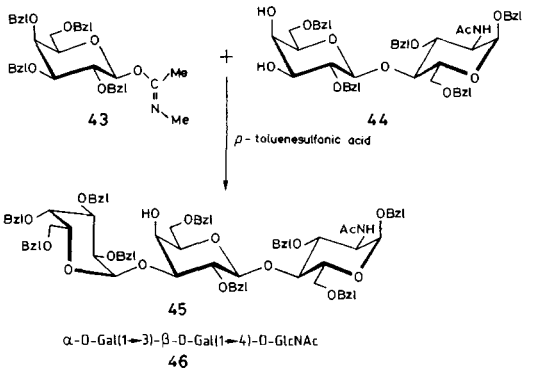
pling step. This strategy may be seen in the synthesis of the pentasaccharide chain **38** of the Forssman antigen[45,46].

Since both galactose units are linked *via* an α-glycosidic link, it is therefore best to couple a trisaccharide halide **35** with a disaccharide hydroxyl component **36,** a lactose derivative. However, special methods are necessary for the preparation and handling of sensitive halides like **35.** The latter is produced from the acetyl derivative and $TiBr_4$ under anhydrous conditions[45,46]. It is thus possible to couple the trisaccharide halide **35** with **36** in the presence of $AgClO_4/Ag_2CO_3$ to give the pentasaccharide **37** in 28% yield[45,46]. Considering the well-known poor reactivity of the 4-OH group of the lactose derivative **36** in reactions with monosaccharides, this is a remarkably good result. Deblocking yields the pentasaccharide hapten **38** of Forssman's antigen. The tetrasaccharide chain of globoside (P-antigen) is synthesized in a similar manner[47].



A further example of a block synthesis is the coupling of the branched trisaccharide halide **39** with the rhamnose derivative **40**[48]. The 4-OH group in **40** is, as already stated, extremely reactive. Since, however, with two specific glycosyl residues the reactivity of the halide **39** can no longer be varied, even use of the mildest possible catalyst, $Hg(CN)_2/HgBr_2$, yields an anomeric mixture of the tetrasaccharides in the ratio of *ca.* 1 : 1, which can, however, be separated[48]. Deblocking the α-glycosidically linked product **41** results in a tetrasaccharide **42,** which represents the repeating unit of the lipopolysaccharide of *Escherichia coli* O75. A spacer is attached to the reducing end, permitting direct coupling with a protein, and in this way a synthetic antigen can be obtained containing the synthetic tetrasaccharide of **42** as determinant.

Imidate method and methods with other leaving groups: Sinay et al.[23,49] discovered that the *N*-methylacetimidoyloxy moiety is a good leaving group for glycoside syntheses. β-Imidates of this type, *e.g.* **43,** can be made by reacting pyranosyl halides with *N*-methylacetamide and freshly prepared silver oxide in the presence of diisopropylamine, and are stable enough to be isolated and stored. They react with hydroxyl components in nitromethane in the presence of *p*-toluenesulfonic acid and a molecular sieve of 4 Å with inversion to give α-glycosides.

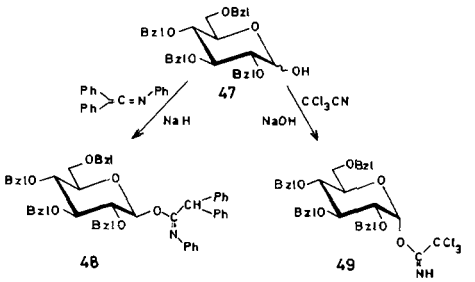


The synthesis of the trisaccharide **46,** which represents a building block of the determinant of the B blood-group substance serves as an example[50]. Under the above conditions, the imidate **43** reacts with the disaccharide **44,** to give, in high selectivity and good yield, the α-glycosidically linked trisaccharide **45,** which can then be deblocked to give **46.** Only the more reactive 3'-OH group takes part in the reaction.

A wide range of oligosaccharides has been prepared in this way[23,49]. Glucose, galactose, and fucose derivatives are suitable for the glycosidation step. The trisaccharide **21**[51] and the tetrasaccharide **24**[52] can also be prepared by the imidate method, when in place of the halides **14** and **22** the corresponding imidate is used for the coupling step.

The disadvantage of the method is that the imidates must first be prepared from pyranosyl halides, from which the desired end product can also be obtained by *in situ* anomerization. The overall yields in both cases are of the same order of magnitude. Furthermore, it should be noted that imidates such as **43** only react well when the sugar moiety contains exclusively benzyl groups *i.e.* the substitution must be such as to produce the highest reactivity at the anomeric center. The presence of even one acyl group in the molecule is sufficient to depress the reactivity to a considerable extent. Attempts to make disaccharide imidates react have so far been unsuccessful[41].

Another suggestion, to prepare an imidate directly from a component such as **47** not substituted at 1-OH, has been made[53a]. With ketenimine a β-imidate **48** is obtained from **47,** whereas with trichloroacetonitrile the product is the α-imidate **49.** Both compounds should be suitable for disac-



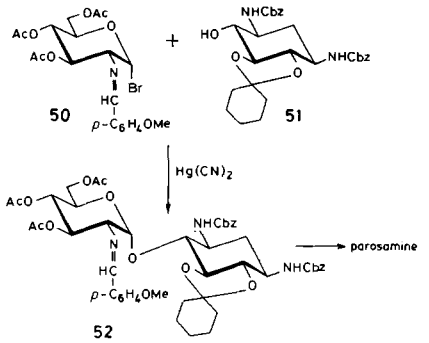
charide syntheses, α-glycosides being produced preferentially from **48**, and β-glycosidic linkages from **49**. It remains to be seen whether the procedure will prove successful and exhibit sufficient selectivity.

Delicate β-glycoside linkages, *e.g.* those of D-mannose[53b] and L-rhamnose[53c] derivatives cannot be produced from α-imidates. In this case α-glycosides are obtained with retention (cf. Section 2.3.3).

Sulfur-containing leaving groups, such as in 1-thio-β-glycosides with (2-pyridyl)-[54], (2-pyrimidyl)-[55], and (2-benzothiazolyl)-1-thio-β-glycosides[56] have been suggested for use in glycoside syntheses. Positively charged leaving groups, such as ammonium groups[57] and 1-*O*-sulfonates[58], have also been investigated. In addition, it has been postulated for reactions in acetonitrile that a nitrilium ion appears as an intermediate which, when reacted further, could be used to steer the glycoside synthesis[55,59]. According to another method, alkali-stable saccharides with a free 1-OH group are converted into their sodium alcoholates, which can then be alkylated to the glycoside with the triflate of the alcohol component[60]. None of these methods has yet found wider acceptance in oligosaccharide syntheses.

2.2.2. 2-Amino-2-deoxy-α-D-glycopyranosides of the *gluco*- and *galacto*-Series

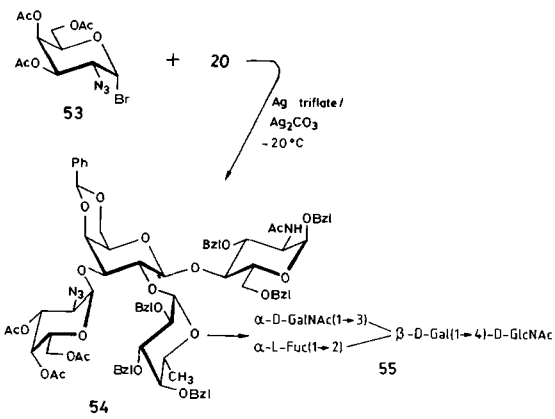
As already discussed in Section 2.2.1, for the synthesis of α-glycosides from 2-amino sugars it is necessary that a non-neighboring-group-active substituent be present at C-2. 2-Acylamino sugars are therefore unsuitable for α-glycoside syntheses. Thus, 3,4,6-tri-*O*-acetyl-2-acetamino-2-deoxy-D-glucosyl halides yield either oxazolines, with involvement of the neighboring group, or preferentially form β-glycosides. The diphenylphosphono group[61] and the 2,4-dinitrophenyl group[62] have proved suitable non-neighboring-group-active substituents on the nitrogen. *p*-Methoxybenzylidene compounds such as **50** have also been used[63].



50 can be converted with the deoxystreptamine derivative **51** in the presence of $Hg(CN)_2$ into **52**, with preferential formation of the α-glycoside; parosamine can be obtained from **52** by deblocking. Dihydrostreptamine[65] and neamine[66] can be synthesized in a similar fashion. It should further be mentioned that many other amino sugars in which the amino group is not bound at C-2 have been used for glycoside syntheses of glycoside antibiotics[63]. For this purpose amino sugars of this kind can be regarded as normal sugars (Section 2.2.1).

The Azide Method: The best method, and one that can be applied to a very wide range of α-glycoside syntheses of 2-amino sugars is, however, the azide method[24-27], in which use is made of 2-azido sugars, which can now be obtained by various methods[24,26,67]. The azido group is a non-neighboring-group-active substituent which is subsequently readily converted into an amino group. In addition, azido sugars have some particularly advantageous solubility properties for glycoside syntheses. The yields and the selectivities are high. The advantage of the method is that 2-azido-2-deoxy-D-glycopyranosyl halides can be converted selectively into α-glycosides both directly as β-halides, or by *in situ* anomerization as α-halides[19]. In the direct process the 2-azido-2-deoxy-α-D-glycopyranosyl halide obtained on halogenation must first be reacted to give the desired 2-azido-2-deoxy-β-D-glycopyranosyl halide in a controlled anomerization reaction using tetraethylammonium halide with acetonitrile as solvent[24]. This reaction can easily be followed polarimetrically and must be terminated by addition of toluene when the maximum proportion of β-halide (highest negative rotation value) has been reached, since otherwise further re-anomerization takes place. The resulting β-chloride then reacts rapidly with the alcohol component in the presence of $AgClO_4/Ag_2CO_3$ under very mild conditions in CH_2Cl_2. The α-glycosides are obtained with good selectivity and in high yields[24]. This method has proved to be of value with reactive hydroxyl components, since with these the selectivity decreases when the *in situ* anomerization method is used.

In situ anomerization is, however, the best method for moderately reactive hydroxyl groups, such as secondary hydroxyls, the same parameters applying as have already

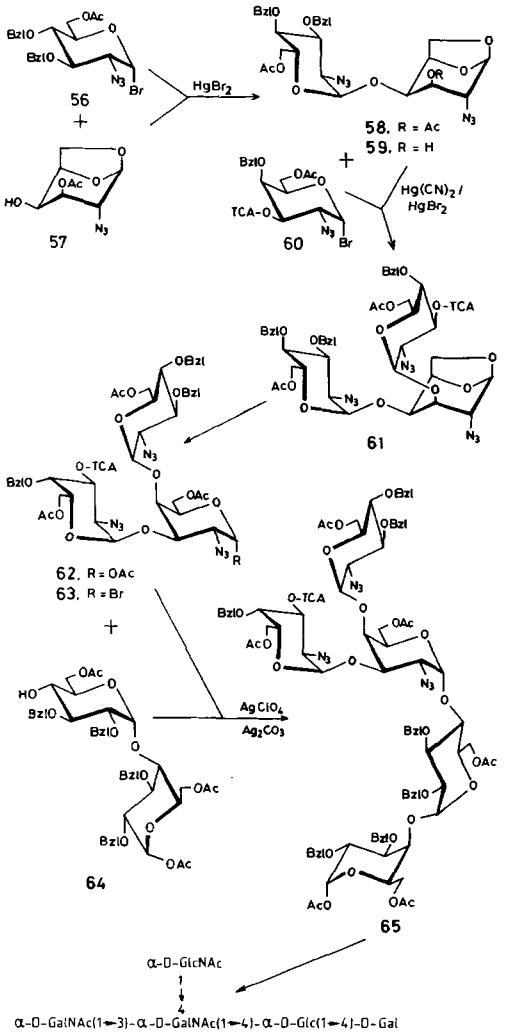


been given for normal sugars in Section 2.2.1. In this instance the reactivity is obviously governed by the nature of the substituents in the pyranosyl halide. As a rule, in comparable reactions somewhat more active catalysts are necessary with the azido sugars compared to normal sugars[21].

The synthesis of the tetrasaccharide determinant of blood-group substance A may be given as an example[21]. The 2-azidogalacto sugar **53** can react with the trisaccharide **20** in the presence of silver triflate/silver carbonate at −25 °C to give a 75% yield of the tetrasaccharide **54**. Deblocking then yields the tetrasaccharide determinant **55** of blood-group substance A. The reaction with silver triflate proceeds stereoselectively at −20 °C, but in contrast, non-

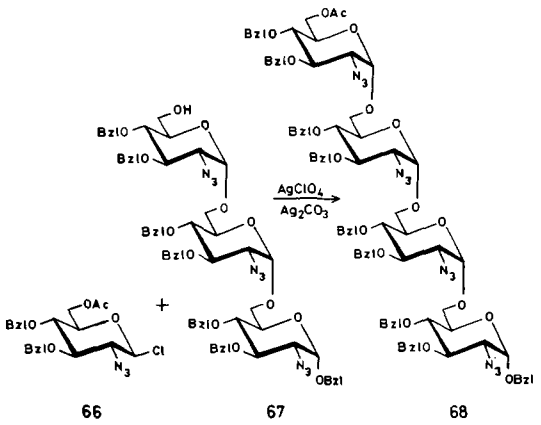
stereoselectively at room temperature, both α- and β-forms being produced. In such cases the catalyst is too active, promoting direct reaction of the α-halide, and hence the catalyst activity must be adjusted exactly.

When the azide method is used with *in situ* anomerization, block syntheses yielding larger oligosaccharide units are also possible. A very good example demonstrating the potential of the method is the synthesis of a branched pentasaccharide[68], which is the repeating unit of the O-specific chain of the lipopolysaccharide of *Shigella dysenteriae* (serotype 2).

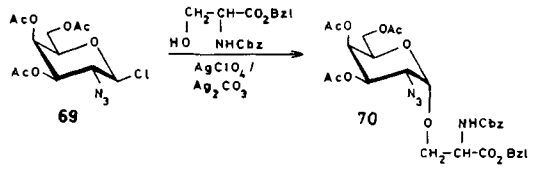


The 2-azidoglucopyranosyl bromide **56** is first coupled with the 1,6-anhydro sugar **57** in the presence of $HgBr_2$ to give the α-glycosidically linked disaccharide **58.** After conversion of **58** into **59** the 3-OH group of the latter can be α-linked with the halide of the galactose derivative **60** (TCA = trichloroacetyl); the branched trisaccharide **61** obtained is acetolyzed to **62,** which can be converted into the corresponding α-bromide **63** with $TiBr_4$[45]. A coupling reaction with the disaccharide **64** with $AgClO_4/Ag_2CO_3$ results stereoselectively in the pentasaccharide **65,** although the 4'-OH group in the disaccharide **64** has extremely low reactivity. Deblocking of **65** then yields the desired pentasaccharide.

In the case of compounds with reactive hydroxyl groups such as the 6-OH group, the OH groups of serine and threonine, and simple alcohols the selectivity decreases in the *in situ* process. The effect cannot be countered by selecting a milder catalyst, because the process of halide ion catalysis with tetraethylammonium halides cannot be used with 2-azido halides. The imidate method is also unsuitable, since the imidates of 2-azido sugars react very poorly. For this reason the β-halides obtained from the α-halides by controlled anomerization must now be used directly. In this way the α-linked tetrasaccharide **68** can be obtained from the trisaccharide **67** — obtained by successive synthesis — using the β-halide **66** and an $AgClO_4/Ag_2CO_3$ catalyst[24].



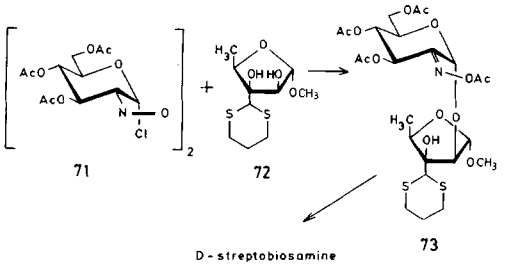
The reaction is particularly difficult with serine and threonine, and a mixture of dichloromethane and toluene must be used together with a β-halide to keep the reaction under control; toluene slows down re-anomerization of the β-chloride to the α-chloride. When a dichloromethane/toluene mixture is used with $AgClO_4/Ag_2CO_3$, the crystalline galactose derivative **69** can be converted into the α-glycoside **70** with high selectivity and in good yield[69]. A corresponding reaction can be performed with a threonine derivative. Both compounds can be converted into disaccharide amino acids by coupling to a galactose residue, these compounds representing the determinants of T-antigen[69].



The Nitroso Halide Method: A completely different method of α-glycoside synthesis has been developed by *Lemieux et al.*[70,71]. Addition of nitrosyl chloride to tri-*O*-acetylglucal produces a nitroso chloride **71** in dimeric form. This can be reacted with hydroxyl components, even those having reduced reactivity, to give α-glycosides. The resultant product is, however, a 2-oxime that, after acylation, must be reduced to an amino compound. In the *gluco*-series this reduction can be performed stereoselectively with diborane, resulting in formation of α-glycosidically linked disaccharides of the glucosamine.

The method may be illustrated using the example of the synthesis of D-streptobiosamine[72]. The nitroso component **71** reacts with the streptose derivative **72** to give, after acylation, 2-oximo-α-glycoside **73.** Reduction of the oxime

with diborane then yields the D-streptobiosamine derivative, from which the free disaccharide can be obtained by deblocking. The synthesis has been used in the same way to obtain natural L-streptobiosamine[72].



A number of modified gentamicin derivatives have also been obtained in this way[73,74]. However, at times a loss of stereoselectivity has also been observed[74,75]. α-Glycosides of galactosamine cannot be produced in this way, since 2-oximoglycosides thus obtained are preferentially reduced to talosamine glycosides.

2.2.3. β-D-Mannopyranosides and β-L-Rhamnopyranosides

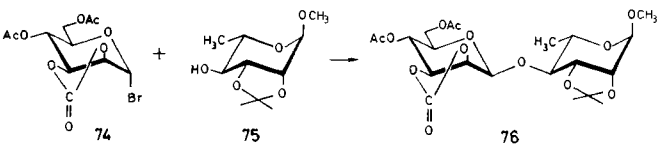
In mannose derivatives the hydroxyl group on C-2, important for guiding the glycoside synthesis, is positioned axially in contrast to the situation in glucose and galactose derivatives. The same applies to L-rhamnose. If a neighboring-group-active substituent is present at 2-OH, an acetoxonium intermediate can form from a mannopyranosyl halide as in reactions **1**→**4**, in which the configuration at C-1 and C-2 is the opposite to that in **4**. Opening this acetoxonium ring by a nucleophile at C-1 then leads to formation of α-D-mannopyranosides. This reaction proceeds well, and it is therefore relatively simple to prepare α-glycosidic linkages with D-mannose. A number of higher mannose oligosaccharides have already been synthesized in this way (Section 2.3.3).

The formation of a β-D-mannopyranosidic link, on the other hand, is the most difficult type of linkage to realize. In the presence of a neighboring-group-active substituent at C-2 only α-glycosides are obtained, but even with other substituents at C-2 formation of α-glycosides is still often the preferred reaction. The difficult problem is the conversion of a relatively stable α-halide, with inversion, into a non-stabilized β-glycoside. An *in situ* anomerization process, such as can be used very successfully in α-glycoside synthesis, is therefore impossible in this case. All the catalysts listed in Table 1 are therefore unsuitable for this glycosidation, since they would promote anomerization to the reactive β-halide, resulting in formation of the undesired α-glycoside as the main product. Therefore, under these conditions α-D-mannosides are obtained from α-D-mannopyranosyl halides without neighboring-group participation.

To avoid these difficulties, elaborate synthetic routes have been traversed[76–79]. A glycoside synthesis was performed using D-glucose with neighboring-group participation which leads relatively easily and stereoselectively to the β-glucopyranoside. The 2-OH of the *gluco*-unit was selectively deblocked, oxidized to the keto group, and then selectively reduced, whereby a β-mannopyranoside was produced. Until very recently[80] this complex route was the only way to solve such problems, particularly that of formation of the β-D-Man(1→4)-β-D-GlcNAc linkage, which occurs in many glycoproteins[78,79].

Only an insoluble silver catalyst should promote the reaction of the α-halide to the β-glycoside, since when the reaction is carried out heterogeneously, anomerization to the reactive β-halide is severely restricted and reaction of the α-halide with inversion takes precedence. However, a halide with the greatest possible reactivity and a hydroxyl group of sufficient reactivity should be chosen, so that selectivity can be retained. With unreactive hydroxyl groups the proportion of α-glycoside increases, and can even become the main product. This constitutes a fundamental limitation of the method and block syntheses would hardly be possible. Silver oxide and the more reactive silver silicate, which is precipitated onto a carrier such as alumina, are considered to be the best catalysts[81].

Reactions with insoluble silver catalysts: The D-mannose derivative **74**[82], reacts with the rhamnose derivative **75** in the presence of silver oxide and a molecular sieve of 4 Å to the β-linked disaccharide **76** in good yield (up to 91%)[82–84]. However, it should be borne in mind that the reactivity of the 4-OH group of the rhamnose derivative **75** is comparable to that of a primary hydroxyl group. When other secondary hydroxyl groups of moderate reactivity are used, the yield on reaction with **74** is considerably smaller[85,86]. As shown in Table 1, the bromide **74** with its numerous acyl substituents is stable and not very reactive, and is thus not universally useful.

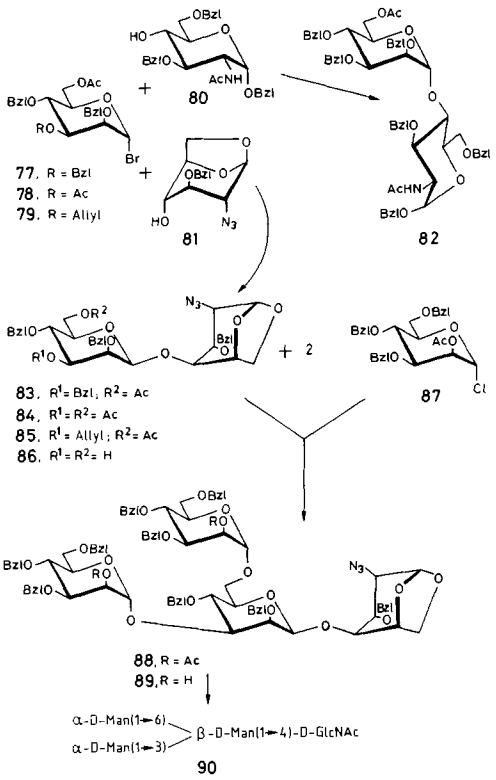


The benzylated compound **77** is much more reactive and reacts with 3-*O*-acetyl-1,6-anhydro-2-*O*-benzyl-D-galactopyranose in dichloromethane, using a reactive silver silicate catalyst, to give the corresponding β-glycosidically linked disaccharide in 70% yield[80].

Reaction of the reactive halide **77** with the glucosamine derivative **80**, present in the $^4C_1$ conformation[*], in the presence of a silver silicate catalyst results in formation of the undesired α-glycosidically linked product **82** in 75% yield. The 4-OH group in **80** is known to have low reactivity, and this has the effect of severely reducing selectivity in the direction of the β-product.

On the other hand, reaction of **77** with the glucosamine derivative **81**, present in the $^1C_4$ conformation, under the same conditions produces the desired β-glycosidically linked disaccharide **83** in up to 60% yield[80]. The α:β ratio is 1:6. If the less reactive halide **78**, which contains two acetyl groups, is allowed to react with the same hydroxyl

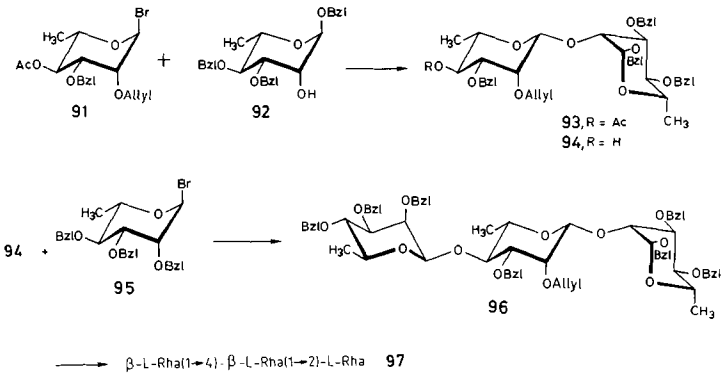
[*] In the $^4C_1$ conformation C-1 is directed below, and C-4 above a plane through atoms C-2, C-3, C-5, O-5 of the chair conformation. In the inverse $^1C_4$ conformation, C-1 is above and C-4 below the same plane. Cf. R. E. Reeves, *Adv. Carbohydr. Chem.* 6 (1951) 107.



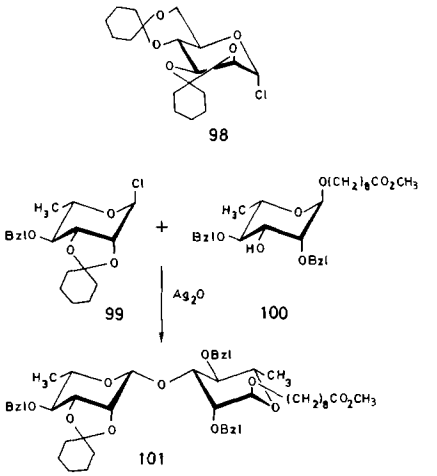
component **81**, only 40% of β-glycoside **84** can be isolated, since the α:β ratio is now only 1:1. This lower reactivity of the halide component is already manifested in a reduction of the selectivity. This demonstrates the importance of the halide reactivity.

Allyl substituents behave similarly to benzyl substituents, since **79** likewise reacts with **81** to give the β-glycoside **85** in 60% yield, corresponding to an α:β ratio of 1:6. Partial deblocking of **85** gives the disaccharide **86**, which under the conditions of α-glycoside synthesis can be coupled in the presence of silver triflate with two mannose residues **87** to give tetrasaccharide **88** in 80% yield[80]. The tetrasaccharide **90**, obtained after deblocking, is the most important key structural element of the carbohydrate chains of glycoproteins and occurs in virtually all glycoproteins with a saccharide-asparagine linkage as branching element; the above method was the first to make it directly accessible synthetically[80].

The behavior of L-rhamnose derivatives is similar to that of D-mannose derivatives. Because of the 6-deoxy group the halides are slightly more reactive, hence further promoting the selectivity of the reaction, but they are more difficult to handle. Many β-glycosidically coupled disaccharides have been produced with the benzylated α-L-rhamnopyranosyl bromides[87,88]. The synthesis of a trisaccharide with two β-glycoside linkages may be given as an example[88]. The bromide **91** is sufficiently reactive to react selectively with the rhamnose derivative **92** unsubstituted at the 2-OH group. In the presence of silver silicate only the β-glycosidically linked disaccharide **93** is obtained, in 70% yield. After conversion of **93** into **94** this reacts further with the bromide **95** at 4'-OH, to give the trisaccharide **96**, with exclusive formation of the β-glycoside in 70% yield. The deblocked trisaccharide **97** is a component of the repeating unit of the lipopolysaccharide of *Shigella flexneri* serotype 6[88].



The D-mannose and L-rhamnose derivatives **98** and **99** have also been proposed for β-glycoside synthesis[89,90]. The spiroketal grouping likewise endows the compounds with good reactivity, so that in this respect they are comparable with the benzyl compounds. The mannose derivative **98** reacts with sugars having primary 6-OH groups and a 4-OH group, known to be equally reactive, to give a good yield (*ca.* 80%) of β-glycosidically linked compounds[89]. However, with less reactive secondary hydroxyls the selectivity decreases, with the result that equal proportions of the α- and β-forms are usually produced. The rhamnose derivative **99**, like the bromide **91**, is somewhat better in relation to its reactivity. Approximately equal proportions of β-glycoside are obtained with both compounds. Coupling **99** with the spacer-containing *rhamno*-derivative **100** gives, *e.g.* in the presence of silver oxide, the β-linked disaccharide **101** in 62% yield[90]. A β-glycoside synthesis with 1-*O*-tosylates of D-mannose has so far only been possible with compounds having the primary 6-OH group[91].



2.3. Formation of 1,2-*trans*-Glycopyranoside Bonds

2.3.1. β-Glycopyranosides of the *gluco*- and *galacto*-Series

This type of reaction represents the oldest type of Koenig-Knorr synthesis[92]. Here, use is made of an α-D-glycopyranosyl halide with a neighboring-group-active substituent, such as acetyl or benzoyl, at 2-OH. In the presence of an insoluble silver catalyst the reaction should assume a

stronger S_N2 character and thus proceed largely with inversion.

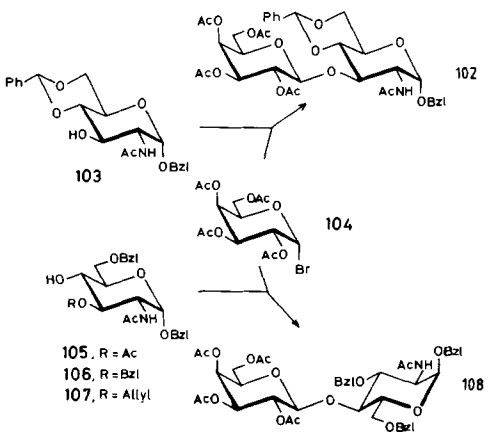
Presumably with soluble silver and mercury catalysts the oxocarbenium ion **3** is formed first, and this then reverts to the more stable cyclic acetoxonium ion **4.** Nucleophilic opening of the ring at C-1 can then only take place as a *trans*-cleavage, the acetoxonium intermediate guiding the reaction in the direction of β-glycoside **5.** Express reference should be made to the fact that the cation **4** is not present in the free form but presumably as an intimate ion-pair. The solvate-separated cation **4** undergoes a sequence of acetoxonium rearrangements with inversion at three C atoms, resulting in the *ido*-configuration[93,94]. Rearrangement products of this type have never been observed in glycoside syntheses proceeding *via* cation **4.**

The starting materials for the β-glycoside synthesis, the α-glycosyl halide or the stabilized acetoxonium ion **4,** are less reactive than the highly reactive β-glycosyl halide, the starting product for α-glycoside synthesis (Section 2.2.1). This can lead to certain difficulties in applying the method to block syntheses.

In principle, it is also possible to form a β-glycosidic link without neighboring-group participation of the substituent at C-2. Surface-active, insoluble catalysts such as silver silicate would have to be used, so that the reaction would proceed cargely by an S_N2 mechanism. The conditions would be similar to those described for the preparation of β-D-mannopyranosides. Because of the difficulties and limitations mentioned in Section 2.2.3, reactions of this kind have not been so thoroughly investigated.

Reactions with Silver or Mercury Catalysts: Insoluble silver catalysts such as Ag_2O and Ag_2CO_3, with which an S_N2-like mechanism is followed, have the disadvantage that water is formed in the course of the reaction, making it necessary to add drying agents such as Drierite. In oligosaccharide syntheses the yields are relatively low, a fact that renders this method rather less suitable.

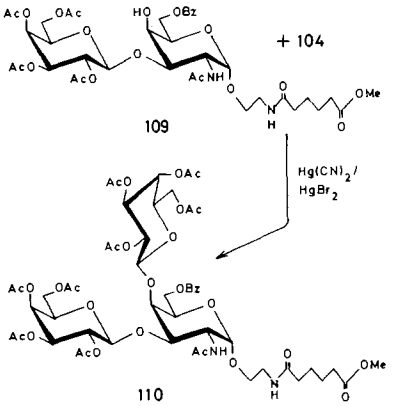
The Helferich catalyst $Hg(CN)_2$ has proved to be very effective[95]. The hydrogen cyanide produced during the reaction is able to escape or does not interfere with the main process, the formation of 1-cyano compounds as by-products being observed only in isolated cases. Since the reaction may proceed *via* an acetoxonium ion **4,** it is best to use a solvent of moderate polarity, such as a mixture of benzene and nitromethane, to facilitate ionization to **4.** It is also recommended that benzene be replaced by the less



toxic toluene. Reactions carried out in toluene/nitromethane mixtures proceed in exactly the same way. If excessively polar solvents are used, the halide easily decomposes. Solvents of low polarity such as dichloromethane are also highly suitable. The solvent ratio is a critical factor that can, in particular, influence selectivity and yield, and must be carefully optimized in each case. With slightly reactive OH groups, considerable proportions of α-glycoside can be formed, presumably because the ion **3** undergoes further, nonspecific reactions. $Hg(CN)_2$ can be activated by addition of $HgBr_2$. In this instance too the ratio of the two catalysts should be carefully adjusted.

A good example of an $Hg(CN)_2$-catalyzed process is the reaction of galactosyl bromide **104** with the glucosamine derivative **103** to give the disaccharide **102,** which in benzene/nitromethane (1 : 1) at 60 °C is obtained in 80% yield[96,97].

The 4-OH group in the glucosamine derivatives **105–107** is substantially less reactive than the 3-OH group in **103.** The importance of the type of substitution in the hydroxyl component is well demonstrated in compounds **105–107**[23]. On the whole, alkyl-substituted compounds (cf. Table 1) should be reactive. Compound **105,** substituted at 3-OH with an acetyl residue, can be converted into a disaccharide with the halide **104** but the yield is very low. The derivatives with *O*-benzyl or *O*-allyl substituents, **106** or **107,** on the other hand, give good results when used in the disaccharide synthesis with **104**[23]. The disaccharide **108** can be obtained from **104** and **106** in the presence of $Hg(CN)_2$ in benzene/nitromethane, although the reaction takes longer than that leading to **102**[21,98]. Using a different technique, the reaction is also possible in dichloromethane in the presence of $HgBr_2$ and powdered molecular sieve 4 Å, the yield then exceeding 70%[50]; the quality of the molecular sieve plays an important part. The disaccharides **102** and **108** are constituents of determinants of blood-group substances.



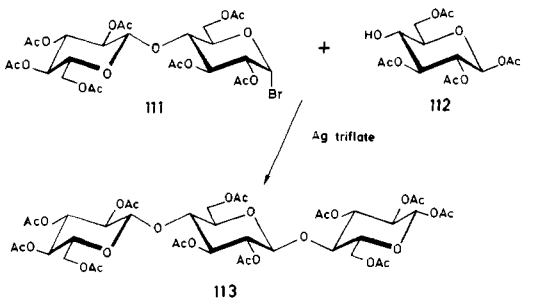
The disaccharide **109** which contains a galactosamine moiety with a spacer unit can be obtained in good yield by appropriate coupling with $Hg(CN)_2$ and addition of $HgBr_2$[99]. A further galactose residue can be coupled to **109** at the less reactive 4-OH group under the same conditions to give the branched trisaccharide **110**[99,100]. The order in which the two galactose residues are added to the galactosamine derivative is important. The disubstituted product **110** is obtained in high yield if the first galacto re-

sidue is coupled at 3-OH and the second at 4-OH. The saccharides **109** and **110** are components of the T-antigen. They can be coupled to proteins *via* the spacer, which allows the preparation of synthetic antigens[100].

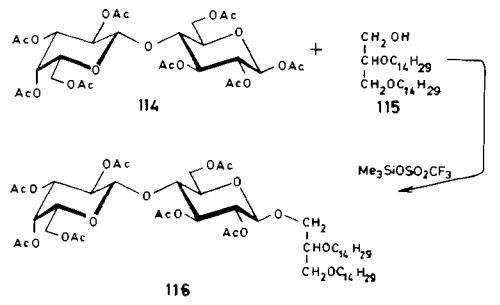
A block synthesis (CH_2Cl_2, $Hg(CN)_2$) has been reported in which the halide of β-D-Gal(1→4)-D-Gal reacts with 3-*O*-acetyl-1,6-anhydro-2-*O*-benzyl-D-glucopyranose[101]. However, during this reaction acyl migration of 3-OAc to 4-OH sometimes occurs, so that a mixture of the desired β(1→4)-coupled product and the undesired β(1→3) product is obtained.

Another reagent highly suitable for use as a promoter in β-glycoside synthesis is silver triflate[102]. The reaction is carried out in dichloromethane at low temperatures (−30 to 0 °C) using equimolar quantities. It is advantageous to add tetramethyl urea or, less advantageously, s-collidine, as acid scavenger. A disaccharide corresponding to **102**[102], or a disaccharide which contains the β(1→4) link as in **110**[103] can be similarly successfully prepared in this way.

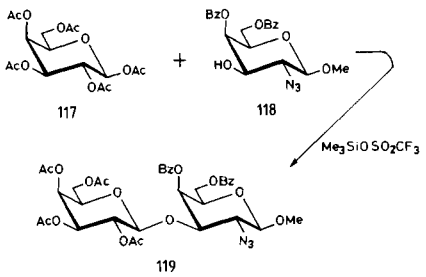
The effectiveness of the silver triflate method is evident in the syntheses of cellotriose derivatives. The very weakly reactive 4'-OH group in an acetylated cellobiose derivative reacts with acetobromoglucose in the presence of silver triflate to form the cellotriose derivative in 53% yield[104]. A block synthesis has also been successfully carried out. The cellobiose bromide **111** could be made to react with the difficultly reactive 4-OH group of the glucose derivative **112.** In the presence of silver triflate 39% of the cellotriose **113** was obtained in 1 h at −30 °C.



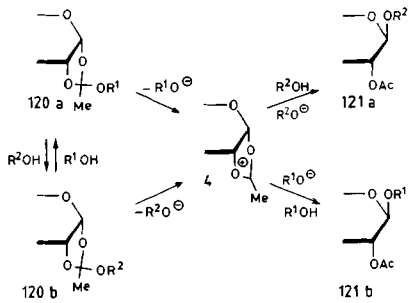
Trimethylsilyl triflate has recently been proposed as a coupling agent for β-glycoside synthesis. In this reaction it is unnecessary to use the halide, and instead the β-1-*O*-acetate itself can be used. Thus, the lactose derivative **114**



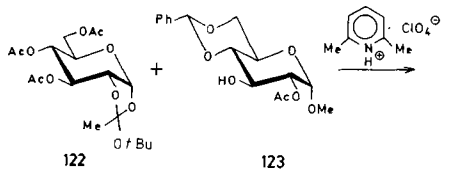
reacted with the glycerol derivative **115** in the presence of trimethylsilyl triflate and molecular sieve 4 Å (20°, 2 h) to give the glycoside **116** in 70% yield[105a]. In the meantime we have extended this technique to reactions with secondary hydroxyl groups[105b]. Penta-*O*-acetyl-β-D-galactopyranose **117** reacts with **118** in the presence of trimethylsilyl triflate to give a 70% yield of the disaccharide **118.** The 3-OH group in **119** has an extremely low reactivity, and a coupling reaction in the presence of $Hg(CN)_2$ or $Hg(CN)_2$/HgBr could only be performed in moderate yield with inadequate selectivity. It is possible that earlier described galactosylation reactions may also be satisfactorily performed by this new procedure.



The Ortho-Ester Method: The cyclic acetoxonium ion **4** occurring as an intermediate during β-glycoside synthesis need not necessarily be derived from pyranosyl halides: it can be produced from ortho-esters by abstraction of an alkoxide anion, *e.g.* with $HgBr_2$. **4** reacts with the hydroxyl component *via trans*-opening to give the β-glycoside.



According to *Kochetkov et al.*[12, 106], two complications arise with the ortho-ester method. The alcohol R^1OH, formed in the cleavage reaction of ortho-ester **120a** to give the ion **4,** competes with the reacting alcohol component R^2OH, and two glycosides **121a** and **121b** can therefore be produced if the R^1OH is not removed from the equilibrium, *e.g.* by distillation. In addition, a transesterification of the ortho-ester **120a** with the alcohol component R^2OH can occur to give the ortho-ester **120b.** However, this can also be converted into the glycoside **121b** *via* the cation **4.** To avoid these difficulties, a *tert*-butyl ortho-ester has proved to be the best starting material, and 2,6-dimethylpyridinium perchlorate the best catalyst. Possible solvents are dichloromethane or, at higher temperatures, chlorobenzene. In this way **122** and **123** can be converted into the disaccharide **124** in about 50% yield[107]. A large number of ortho-esters have been prepared and reacted[106]. Polysaccharides with about 10—30 saccharide units can also be made in this way using compounds containing an ortho-ester and a hydroxyl group in the same molecule[12, 106].



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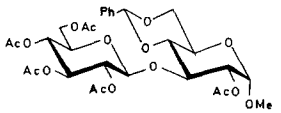
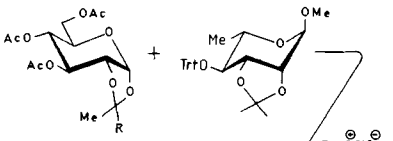


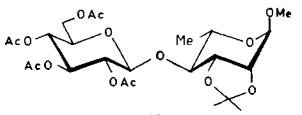
124

Nevertheless, the ortho-ester method is critical with weakly reactive hydroxyl groups. This is shown by the preparation of the lactosamine derivative **108**[108]. The ortho-ester method, in which a *tert*-butyl ortho-ester activated by benzyl-group substitution is actually used, yields 52% of β-glycoside **108**, 12% of the α-glycoside is also formed. With $Hg(CN)_2$ or $HgBr_2$ a 70—80% yield of β-glycoside **108** is obtained[21, 50].



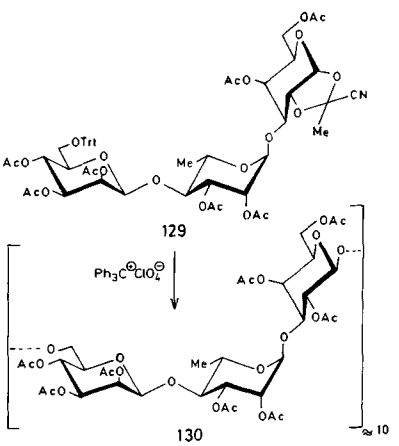
125, R = CN
126, R = p-MeC$_6$H$_4$S

127



128

The ortho-ester method can be modified using the 1,2-cyano compound **125**[109, 110] or the thio-ortho-ester **126**[111]. The alcohol component must, however, be used as a trityl ether. The Meerwein reagent triphenylcarbenium perchlorate serves as a catalyst. The triphenylcarbenium ion cleaves off the nitrile group from **125** and the thiol group from **126**, in both cases with formation of the cyclic acetoxonium ion **4**. The latter then reacts irreversibly with the trityl ether **127** to form the β-glycoside **128** and a tritylcarbenium ion, which is subsequently regenerated. In this way only catalytic quantities of triphenylcarbenium ion are necessary, and no perchloric acid is formed[110, 111]. By means of this method **125** can be converted into the disaccharide **128**, however, the 4-OH group of the rhamnose is so reactive that **128** can also be obtained by many simpler methods. By using the modified orthoester process, the rhamnose and galactose derivatives can also be coupled *via* the 2-OH and 3-OH groups, respectively[110]. On the other hand, the reaction with weakly active 4-OH groups does not proceed to completion. Compared to other direct methods, it should be noted that the derivatives **125** and **126** must be made from pyranosyl halides and the production of the trityl ether—often a difficult process—requires an additional step.



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130

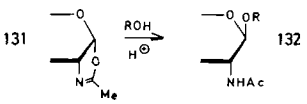
The modified ortho-ester method is primarily of interest for polysaccharide synthesis[112]. Trisaccharide **129** reacts with triphenylcarbenium perchlorate to give polymer **130** containing about ten trisaccharide units per molecule. The trisaccharide β-D-Man(1→4)-α-D-Rham(1→3)-β-D-Gal contained in **130** is the repeating unit of the O-antigenic lipopolysaccharide of *Salmonella newington*.

2.3.2. 2-Amino-2-deoxy-β-D-glycopyranosides of the D-*gluco*- and D-*galacto*-Series

In the case of the 2-amino sugars the substituent at C-2 is likewise of decisive importance for the course of the glycoside synthesis. The acetylated pyranosyl bromide of a 2-acetamido sugar is extremely labile and *via* neighboring-group participation can be converted into a 1,3-oxazoline **131**[113]. In contrast to the acetoxonium intermediate produced with normal sugars, the more stable oxazolines can be isolated. The acetylated pyranosyl chloride of a 2-acetamido sugar is considerably more stable, and with it β-glycoside syntheses can be carried out on reactive 6-OH groups in the presence of $Hg(CN)_2$[114].

If a non-neighboring-group active substituent is present at C-2, as in the acetylated pyranosyl halides of dichloroacetamido- and 2,4-dinitrophenylamino sugars, β-glycoside links can also be formed with compounds having 6-OH groups[115, 116]. However, the yield and the selectivity fall off drastically if derivatives with secondary hydroxyl groups are used for the glycoside synthesis[117]. It is therefore recommended to use the tried and tested methods described in the next section.

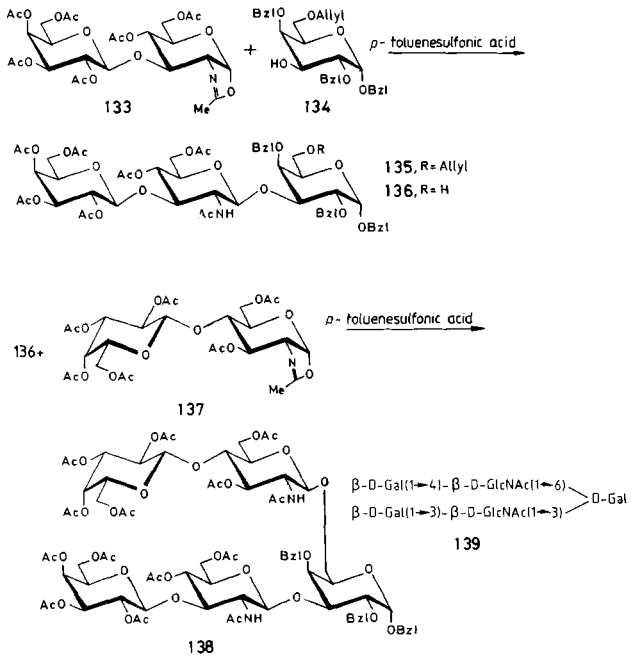
The Oxazoline Method: The oxazolines **131**, accessible from the pyranosyl halides, can be attacked by hydroxyl components at C-1, similarly to the acetoxonium intermediate **4**, whereby β-glycosides **132** are formed stereoselectively. The reaction is carried out in nitromethane/benzene and sometimes in dichloromethane using *p*-toluenesulfonic acid as catalyst[118].



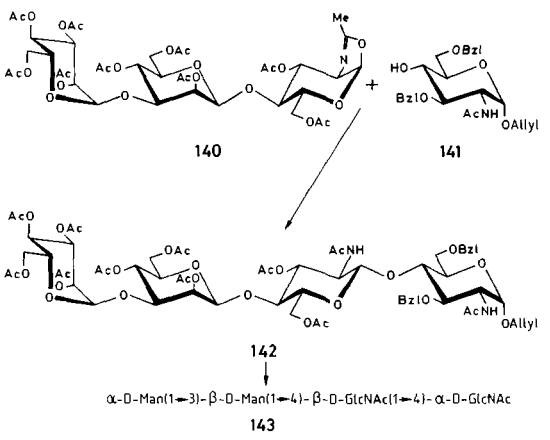
131 132

Newer methods have since been described for the production of oxazolines. Thus, β-1-*O*-acetates can be converted into oxazolines with $FeCl_3$[119], and propenyl glycosides, obtainable by rearrangement from allyl glycosides, are similarly converted using $HgCl_2$[120, 121]; oxazolines are, therefore, readily accessible. A large number of disaccharides has been prepared by the oxazoline method[118]. Very good yields are obtained with 6-OH groups[122, 123], and

even with secondary hydroxyls the yields are still satisfactory[123, 124]. Weakly reactive 4-OH groups can also be reacted. Thus, a chitobiose derivative has been synthesized in 43% yield[125].



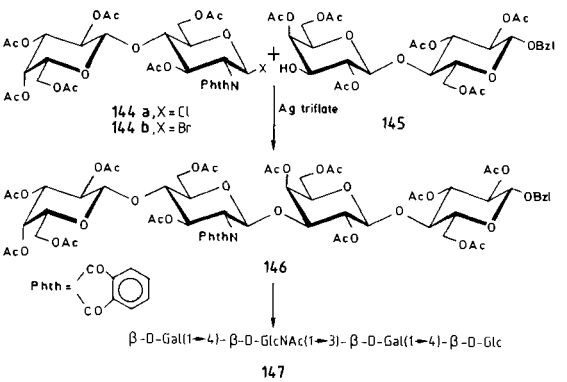
Block syntheses are advantageously carried out by the oxazoline method, *e.g.* with the oxazoline of the lactosamine **137** and the corresponding β(1→3)-linked disaccharide **133**[126]. The oxazoline **133** can be linked to the 3-OH of the galactose derivative **134** by heating in nitromethane/benzene in the presence of catalytic quantities of *p*-toluenesulfonic acid to give the trisaccharide **135.** After deblocking to give **136,** the oxazoline **137** can be linked to the trisaccharide **136,** resulting in the branched pentasaccharide **138**[126]. The yields lie between 50 and 70%. The oligosaccharide **139** obtained from **138** includes structures that occur in the blood-group substances Ii. Coupling with the oxazoline **133** is not without its problems; for example, the 3-OH group in mannose reacts only with difficulty[127].



In the meantime a trisaccharide-oxazoline **140** has been synthesized. Coupling **140** with the 4-OH group of **141** in dichloromethane gave the tetrasaccharide **142** in 22% yield[128]. This is a remarkable result, since the 4-OH group of glucosamine is known to be extremely weakly reactive. The tetrasaccharide **143** constitutes the saccharide chain by which asparagine-linked glycoproteins are connected to the peptide residue.

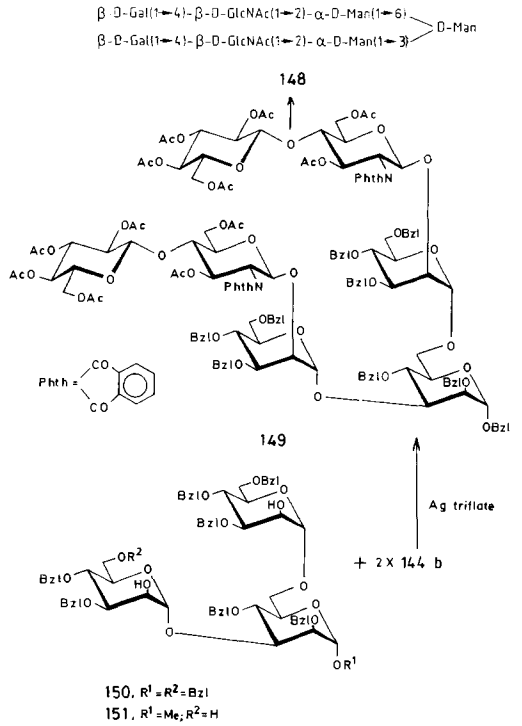
The Phthalimide Method: In addition to the oxazoline method, the phthalimide method has proved to be an effective method for β-glycoside synthesis from 2-amino sugars. A phthalimido group at C-2 is sterically demanding and favors the β-form. It is attributed neighboring-group activity in glycoside synthesis, which causes the reaction to be guided in the direction of the β-glycoside[129]. The reaction is performed at −50 to −20 °C in dichloromethane using silver triflate in the presence of s-collidine as catalyst. The phthalimido residue is cleaved off by hydrazine at higher temperatures during deblocking of the resultant oligosaccharide, a treatment not entirely free from problems if the oligosaccharide is sensitive to alkali.

A number of disaccharides have been synthesized by this method[129]. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl bromide can be linked to the 2-OH group of rhamnose or rhamnose trisaccharides in 70% yield[130, 131]. The phthalimide of the glucosaminyl chloride has been coupled to the extremely weakly reactive 4-OH of muramic acid to give muramic acid disaccharides in 38% yield[132].



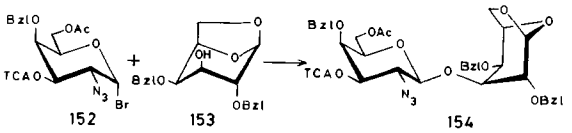
The phthalimide method is evidently also well suited for block syntheses[133]. The phthalimide of the lactosamine **144a** can be linked to the 3-OH group of the lactose derivative **145,** to give the tetrasaccharide **146** in 83% yield. This tetrasaccharide is the carbohydrate chain **147** of the paragloboside of a glycolipid. A similar reaction has also been performed using the oxazoline method[134] giving **146** in 79% yield, so that the phthalimide process can be regarded as somewhat more effective. Coupling to the weakly reactive 4-OH group in lactose has not yet been reported; this is an unsolved problem which is of importance with respect to the formation of biologically relevant oligosaccharides.

A block synthesis with the lactosamine derivative pyranosyl bromide **144b** could be used to synthesize larger oligosaccharide units. The mannose trisaccharide **150** reacts with **144b** (molar ratio 1:2) in the presence of silver triflate, whereby the branched heptasaccharide **149,** a key structure in the carbohydrate part of glycoproteins, is obtained. It contains a branched mannose trisaccharide unit carrying two lactosamine "antennas". This is a remarkable



result. Further syntheses of biologically interesting oligosaccharides can undoubtedly be expected in this sector.

Other Methods: 2-Azidopyranosyl halides, if they are sufficiently reactive, can also be converted into β-glycosides. The active silver silicate catalyst must be used so that the reaction proceeds in the heterogeneous phase. The conditions correspond to those in the β-glycoside synthesis of mannose derivatives (cf. Section 2.2.3). The azido sugar **152** has been coupled with the galactose derivative **153** in dichloromethane at $-20\,^{\circ}C$ to give the disaccharide **154** in 73% yield[46,47]. The disaccharide **154** is an important constituent in the synthesis of the tetrasaccharide chain of globoside (P-antigen)[47].

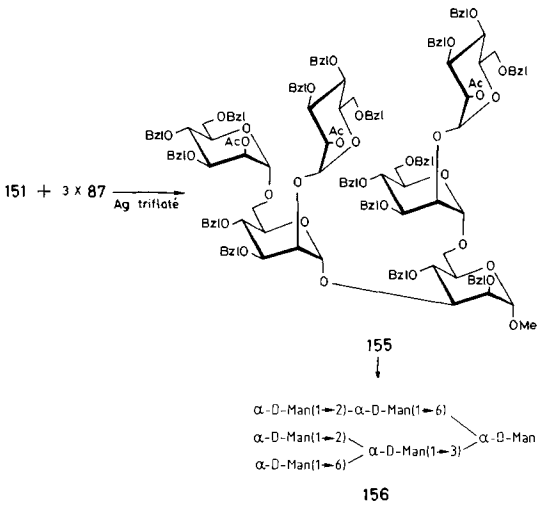


A new disaccharide synthesis, starting from β-1-*O*-acetyl derivatives of 2-acetamido sugars, has recently been reported[136]. 2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose and 1.5 moles of $FeCl_3$ in dichloromethane, in the presence of tetramethylurea react with various saccharides containing free hydroxyl groups to give disaccharides. In the reaction with 6-OH the yield of β-linked disaccharide is about 80%; with 3-OH and 4-OH the yields are, respectively, *ca.* 60 and 40%. The reaction may proceed *via* an oxazoline-like intermediate. It is certainly worth looking into the possibilities of extending this method.

2.3.3. α-D-Mannopyranosides and α-L-Rhamnopyranosides

Similar prerequisites apply to α-glycoside synthesis in the D-*manno*- and the L-*rhamno*-series as to the β-glycoside synthesis in the *gluco*- and *galacto*-series; only the configuration at C-2 is inverted. In glycoside synthesis supported by neighboring-group participation, an inverted acetoxonium ion similar to **4** is formed, which in this case leads selectively to the α-glycoside as a result of *trans*-opening of the ring. Accordingly, the methods are similar to those used for the β-glycoside synthesis of D-glucose and D-galactose. The D-mannose and L-rhamnose halides are highly reactive, and α-glycosidic saccharide links can therefore be readily prepared. Considerable advances have been made in this field in the synthesis of larger oligosaccharide units.

Reactions with Mercury and Silver Catalysts: In addition to $Hg(CN)_2$[137], mixtures of $Hg(CN)_2/HgBr_2$ in the ratio of 1 : 1 have proved to be suitable catalysts favoring coupling reactions[138]. Using these mixtures the trisaccharide **150,** consisting of three mannose residues, can be prepared in *ca.* 50% yield by reacting a D-mannose derivative unsubstituted at 6-OH and 3-OH with 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-mannopyranosyl chloride in toluene/nitromethane[138]. A similar reaction proceeds more advantageously with silver triflate in the presence of tetramethylurea in dichloromethane and an excess of the mannopyranosyl halide. In this reaction the tetrasaccharide **88** is obtained in 80% yield from the disaccharide **86** by attaching two mannose residues[80]. This is the branched key unit of a large number of glycoproteins.

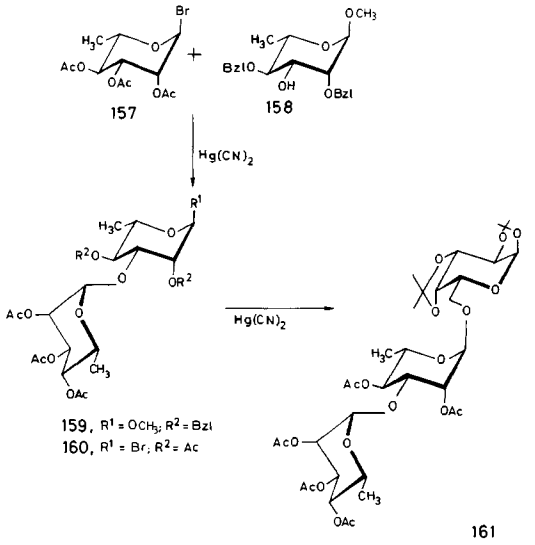


The silver triflate method has proved very effective in connecting several mannose residues. Three further mannose residues can be connected to the mannose trisaccharide **151** *via* three free hydroxyl groups in a single step to give the hexasaccharide **155** in 60% yield[139]. The free hexasaccharide **156** is an important constituent unit of glycoproteins containing mannose chains.

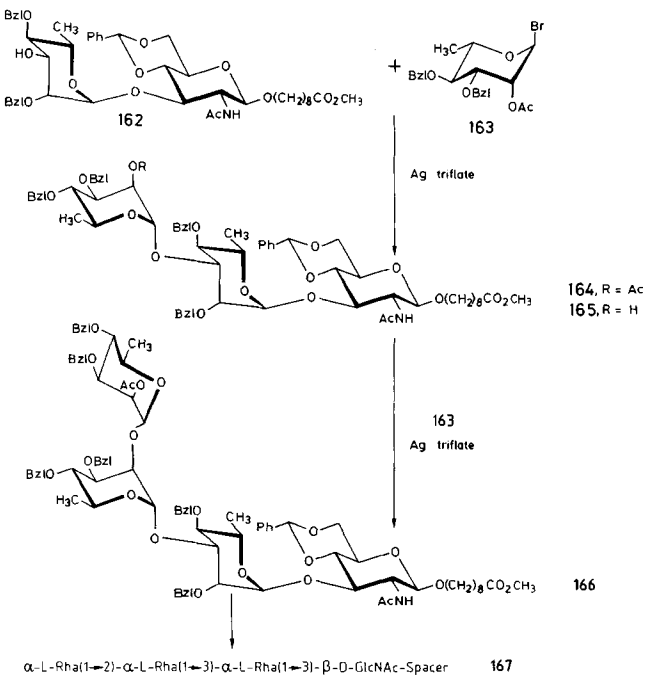
This procedure of simultaneously attaching several mannose residues has also been applied, with astonishing success, to the synthesis of further mannose-containing oligosaccharides. A hexasaccharide slightly modified relative to **155,** consisting of six mannose residues[140], and a number of related pentasaccharides[141,142] have already been synthesized.

The α-glycosidically linked oligosaccharides of L-rhamnose are of considerable interest because they occur rela-

tively widely in the repeating units of a very wide range of lipopolysaccharides. Reactions of the halides with hydroxyl components give the corresponding disaccharides in very good yields using $Hg(CN)_2$ in benzene/nitromethane. In this way the L-rhamnose disaccharides with a 1,2-linkage can be obtained in 95% yield, those with a 1,3-linkage in 78% yield, and those with a 1,4-linkage in 67% yield[143-145]. Block syntheses with rhamnose disaccharides have also been carried out. The 1,3-linked rhamnose disaccharide **159**, obtained by reaction of the halide **157** with **158**, has been converted into the halide **160** and then coupled with the 6-OH of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose to give the trisaccharide **161**[146]. Other examples are also known[147].



Among the oligosaccharide units in lipopolysaccharides those of *Shigella flexneri* have, in particular, been synthesized. The silver triflate method proved highly successful in this instance. The disaccharide **162** from D-glucosamine and L-rhamnose can be coupled at 3'-OH by reaction with the halide **163**, resulting in the trisaccharide **164** in 61% yield. After conversion of **164** into **165** a further L-rhamnose unit can be coupled to give the tetrasaccharide **166** in 70% yield. Other oligosaccharides, containing sequences from the chain **167** or shifted sequences, have likewise been synthesized[149-151].



The glucosamine unit of the tetrasaccharide **167** carries a spacer, which permits coupling to a protein. In this way a synthetic antigen, which contains the tetrasaccharide unit **167** as an immunological determinant, is obtained. Using this antigen, antibodies can be produced in experimental animals. These antibodies produced are directed against bacteria containing the tetrasaccharide unit **167** as a repeating unit in the immunodominant O-specific side chains of their lipopolysaccharides. They would be suitable for therapeutic or diagnostic purposes.

3. Future Prospects

The examples selected were intended to demonstrate the progress that has been made in the field of oligosaccharide synthesis, and to show how important it is to synthesize biochemically interesting, selectively linked oligosaccharide sequences.

There is no doubt that this area of carbohydrate chemistry will increase in significance in the coming years, and in so doing will expand further. Henceforth, the novel synthetic methods should be used to prepare larger oligosaccharide units; thereby, prefabricated synthetic blocks, *e.g.* disaccharide units, will presumably be used in future to a greater extent. Investigations may help to provide further information on the many functions of glycoconjugates, in particular the glycolipids and glycoproteins.

The interactions of the oligosaccharide determinants, *e.g.* in antigen-antibody reactions and receptor effects, may prove to be of particular interest. Empirical and semiempirical calculations have already given some very good indications of the preferred oligosaccharide conformations, and using high-field NMR spectroscopy it has been possible to make statements on conformations of oligosaccharides in solution. Both methods indicate that oligosaccharides do not exhibit great flexibility, and that to a large extent specific conformations are preferred by molecular interactions[152]. Information thus obtained on the topology of determinants, makes it possible to investigate which regions are bound to protein molecules. According to present findings and considerations, the bond may arise not so much from hydrogen bonds as from hydrophobic interactions[152, 153]. Hydrophobic parts of the protein are thus thought to be bound by hydrophobized parts of oligosaccharides. In the complex it is thought that after water has been removed the hydroxyl groups of the oligosaccharide are bound by intramolecular hydrogen bonds in such a way that a hydrophobic face of the oligosaccharide capable of forming a bond is formed. These problems will obviously be the subject of further stimulating work.

A considerable portion of this review is based on results obtained by my colleagues. I should like to thank the team who

worked jointly on the "Oligosaccharide Synthesis" project with Elan for their unremitting efforts and their determination and staying power in the solution of this very difficult problem. Thanks are due particularly to M. Armbrust, A. Bünsch, H. Bünsch, J. P. Hölck, Č. Kolář, W. Kutschker, R. Lebuhn, O. Lockhoff, H. Nürnberger, M. Paal, D. Schnell, and W. Stenzel.

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Single-Phase Polymer Alloys of Polyvinyl Chloride and New Polymers

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Dedicated to Prof. Herbert Grünewald on the occasion of his 60th birthday

Polymer alloying is acquiring ever increasing significance for the modification of polymeric materials. Polymer alloys are defined by their phase character, which in turn is determined by the mutual compatibility or incompatibility of the components. Suitable techniques for the analysis of the phase character include, *inter alia*, dynamic-mechanical methods, according to which a polymer alloy may be considered in a simplified manner as single-phase when only *one* glass transition is observed, even if it extends over a broader temperature range than in the case of the pure components. Aliphatic (polyester)-polycarbonates and tetramethylbisphenol-A polycarbonate are new, PVC-compatible, polymer modifiers. The (polyester)-polycarbonates (from adipic acid, hexane-1,6-diol, neopentanediol, and diphenyl carbonate) yield with PVC single-phase alloys that at temperatures above the glass transitions of the mixture display the characteristics of soft PVC and that are tough far below this temperature. The special high-temperature properties of the resin-like tetramethylbisphenol-A polycarbonate permits the preparation of alloys with increased dimensional stability under heat (higher deflection temperatures under load).

1. Introduction

Single-phase polymer alloys are mixtures of structurally different but mutually compatible polymers. In ideal mixtures of this kind there should be no abrupt change in any physical characteristic along any one spatial coordinate. No structural parameter (*e.g.* density, average molecular weights, impurities, chemical composition) is appreciably dependent upon local variation; however, the usual fluctuations in the structural parameters of the components are also present in the mixture.

The forerunners of the single-phase polymer alloys of today were single-phase mixtures made from a polymer and a low-molecular compound. The first examples of technical significance contained cellulose esters as the polymer component. The plasticization of nitrocellulose[1] with camphor (1870) initiated much extensive research and development work on the synthesis, structure, and application of single-phase polymer mixtures.

Plasticization with low-molecular compounds constituted an important stage in the development of thermoplastic processing of polyvinyl chloride (PVC) on an industrial scale. However, the many advantageous properties of PVC as a material can only be utilized when its limited thermal stability is increased by polymer-specific stabilizer systems[2] and when the difficulties of processing ensuing from its rheological properties[4,5,33] are overcome by the use of processing aids[6].

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2. Scientific and Technical State of the Art of PVC Modification

It has been known since 1933[3] that PVC can be mixed with compounds such as di(*o*-nitrophenyl) ether, dibutyl phthalate, or tricresyl phosphate to give single-phase products (soft PVC types). Many other suitable low-molecular and high-molecular compounds have since been found. The addition of a plasticizer, *i.e.* a plasticizing modifier, generally causes a reduction in the elasticity modulus of amorphous polymers. Since the glass transition temperature of the polymer is lowered by the added component, thermoplastic processing of the mixtures becomes possible at lower temperatures.

While major efforts have primarily been aimed at practicable plasticizing modifiers, in recent years modifiers capable of extending the range of application of PVC to temperatures greater than 70 °C have aroused considerable interest in the industrial sector.

Unmodified PVC has a heat deflection temperature of up to 75—80 °C (Vicat B), a notch impact strength of 2 kJ/m^2 (at room temperature), and a Shore-D-hardness of over 80. By using impact-strength modifiers[7-9,15], multiphase polyblends (see Section 2.1) can be produced that have a notch impact strength varying between 2 and more than 40 kJ/m^2. We shall not go into closer details of the research that has resulted in this state of the art[11].

PVC alloys with an elevated heat deflection temperature under load and soft, flexible plastic alloys with improved low-temperature properties are likewise of potential industrial interest. The range of applications of PVC could be extended by these alloys if it were possible to transcend the present state of the art.

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2.1. Physicochemical Principles

Polymer alloys are mixed systems made by intimate mixing of at least two structurally different polymers. *Plastic alloys* or polyblends contain, in addition, the aids necessary for technical applications, such as stabilizers, antioxidants, and light-protection agents[10]. An essential feature for the manufacture of single-phase polymer alloys is a mutual compatibility of the components.

Polymers of different composition or structure are in most cases not miscible homogeneously—*i.e.* cannot be molecularly dispersed in each other—in any given ratio, but exhibit regions of miscibility gaps. This means that polymers are normally mutually incompatible in mixtures and that single-phase polymer mixtures constitute an exception. The extent of miscibility (or incompatibility) depends on the composition of the polymer mixture, on temperature, and on the molecular weights of the polymer components.

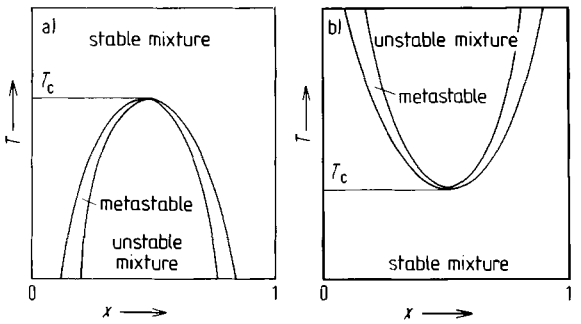


Fig. 1. Idealized phase diagrams for two-component polymer mixtures with a) upper, and b) lower critical solution temperature T_c (after [58]). x = mole fraction.

Figure 1 shows idealized phase diagrams characterizing the typical mixing behavior of two polymers. Above (Fig. 1a) and below (Fig. 1b) a critical temperature T_c the polymers are miscible in all proportions and form stable, single-phase mixtures. If the temperature falls below T_c or rises above T_c (upper and lower critical solution temperature), the two-component system may exist as a stable, as an unstable, or as a metastable mixture, depending on its composition[43].

The thermodynamic explanation for the normally incomplete miscibility of polymers is that mixed polymer systems almost invariably have a strongly positive free energy of mixing ΔG_m. It can be deduced from the basic equation:

$$\Delta G_m = \Delta H_m - T\Delta S_m$$

that ΔG_m only becomes negative or assumes small values when the entropy term $T\Delta S_m \geqq \Delta H_m$. In the case of the mixing of high-molecular compounds, however, the possible increase in entropy is small because only a small number of molecules are being mixed, whereas the mixing enthalpy ΔH_m is much the same as that for structurally similar low-molecular compounds[12-14]. The result is a high positive free energy of mixing in nearly all cases. Only when enthalpic effects are effectively absent, owing to minimal interaction between chain segments of the components, does the relatively small entropy increase suffice for $\Delta G_m \leq 0$. In these special cases molecular dispersion of the two polymers in each other is the energetically most favored state, and only then can mixtures of this type be thermodynamically stable.

The aim of these considerations was to answer, without resorting to experimental evidence, the question whether two or more given polymers would be miscible under specific conditions, and if so, under which? A quantitative equation must thus be given for the change in free energy ΔG_m. Starting out from the criteria for liquid polymer mixtures[12,39-41], it is usual to consider for ΔG_m an equation that essentially contains the polymer-specific Huggins interaction parameter, which is difficult to determine in solvent-free systems. A comparatively precise estimation is possible with the aid of the solubility parameters introduced by *Hildebrand et al.*[42] (summaries in [43-45]). ΔG_m has a mean value when the interaction parameter is at a minimum, and this occurs when the solubility parameters of the two polymers to be mixed are the same. These thermodynamic theories are still rarely used in the solution of practical problems, among other reasons because the requisite thermodynamic data are only adequately known in a few cases, the mathematical work is considerable, and the agreement between theory and practice is only semiquantitative. The solubility parameters or their components assigned to individual interaction forces are often used only for an approximation to the mixing behavior of two polymers. Detailed experimental investigation of the mixing behavior of the alloy components is indispensable; in particular, investigation of the mixture's stability as a function of various parameters, *e.g.* the thermomechanical history of the polymer mixture in question, is of major importance.

Many methods are known to give information on the mutual compatibility of polymers in a mixture, and thus to decide whether one is dealing with a single-phase or a multiphase system. For this purpose practically all the methods of polymer physics normally applied to the study of solid polymers can be used[46,47], the most important being an evaluation of a mixture for transparency, morphological investigations with the aid of optical and electron microscopy, techniques for the investigation of softening behavior (including all methods for studying glass and melt transitions), scattering methods (light scattering, X-ray scattering, neutron scattering), and the determination of surface tensions. For characterization and quantitative testing of the polymer mixtures under investigation we chose to use dynamic mechanical measurements for the determination of the glass-transition temperatures T_g. In these experiments the precondition was that single-phase mixed systems exhibit only *one* glass-transition temperature, which depends only on the proportions of the components present in the mixture. The axiom that *one* glass transition temperature T_g means a *single*-phase system holds true when the glass transitions of the mixture's components are sufficiently far apart. The glass transition is also frequently used as a characteristic parameter of a single-

phase system because it provides particularly valuable information about the potential range of application. Whereas by special phase construction multiphase systems can assume properties not exhibited by any of the starting components, this is obviously by definition impossible with single-phase systems. In general, single-phase polymer alloys can be characterized in respect of their material properties by the relative position of T_g (Table 1).

Table 1. Glass transition temperatures T_g and material properties of polymer alloys (M) made from the components A (main component) and B (modifier).

Material	Relative position of T_g	
Flexible polymer alloys, *i.e.* plasticized materials	$T_gA > T_gB$	$T_gM < \begin{matrix}\text{working}\\ \text{temperature}\end{matrix}$
Polymer alloys with improved heat deflection temperatures useful at elevated use temperatures	$T_gA < T_gB$	$T_gM > \begin{matrix}\text{working}\\ \text{temperature}\end{matrix}$

A PVC modifier must contain polar groups in order to be capable of solvating polyvinyl chloride chains. The modifier as an alloy component is the more effective, the more strongly it increases or decreases T_g when it is present in a specified quantity.

The above-mentioned dynamic mechanical methods of investigation use free or forced oscillations in the linear viscoelastic deformation range to determine the components of the complex modulus, usually as a function of temperature. Starting from low temperatures, the storage modulus (real part) decreases by several orders of magnitude when the temperature exceeds the glass transition region, while the loss modulus (imaginary part) passes through a maximum. Below the glass transition there are further maxima in the loss modulus, which generally are not as high as at the glass transition and which are assigned to secondary relaxations caused by migration of parts of the main chain or of side groups of the polymer molecule (see *e.g.* [48]).

According to this technique, polymer alloys made from mutually incompatible components have several glass transition regions corresponding to those of the pure components. Small temperature differences, frequently observed in such cases, indicate the occurrence of slight phase interactions[49] in the mixed system or partial compatibility of the components.

In compatible mixtures ideally there is only one glass transition, which, in the case of a molecular-dispersive mixing of the components, should be as sharp as in the individual components. However, a broadening of the glass transition range is often observed; this can be explained by the fact that several mixed phases are present, differing slightly in composition only. There is indeed compatibility, but in this case the polymer mixture cannot be regarded as a single-phase system in the strictest sense, as can also be demonstrated *e.g.* by scattering measurements[34]. In this sense the term "single-phase character" used here should be modified. We will use the expression "single-phase systems" for those mixtures that exhibit only *one* transition in the modulus in dynamic mechanical measurements, even if this transition extends over a broader temperature range than in the case of the pure components.

2.2. Single-Phase PVC Alloys

Beginning with the discovery of the first plasticizer for PVC in 1933[3] research and practical experience have yielded a very extensive volume of data on single-phase PVC mixtures[16]. Whereas at first purely empirically usable modifiers were sought and found, increased attention was subsequently paid to the extended theoretical knowledge of the morphology of polymers and of polymer structures. It was found that the PVC-manufacturing process and the polymerization conditions can influence both the fabrication of the PVC alloys and their final properties. A decisive factor in the selection of the most advantageous conditions for the processing of PVC to valuable polymer alloy is, for example, the morphology of the polymer particles, which varies considerably depending on the polymerization process used. In other words, the particle-size distributions of the PVC powder or emulsion and the fine structure of the powder[17-20,31,36,37] are of major importance in the selection of suitable types of PVC. Some important alloy properties also depend on the molecular weight of the PVC[21]. Intensive efforts have been made to correlate the constitution of plasticizers or plasticizing modifiers and their physical properties with the "plasticizer efficiency" or with their technical usefulness as an alloy component for PVC[28-30].

To gain a better understanding of the final properties of single-phase PVC alloys and of the dependence of these properties on the structure of modifiers, it is useful to begin by looking at the structure of polyvinyl chloride and of single-phase PVC alloys. In contrast to the completely amorphous polymers, such as the commercial polystyrenes or polymethyl methacrylates, polyvinyl chloride contains relatively low concentrations of ordered structures[22-27], which some authors even regard as crystalline fractions. However, these ordered structures are present in such small quantities, or have such small dimensions, that their exact and convincing description has so far proved impossible. What seems certain is that as a consequence of the existence of pronounced physical interactions in PVC there are stronger interactions with low-molecular and high-molecular foreign molecules than is the case in mixtures of other amorphous polymers and comparable components. The mode of action of the plasticizers in PVC mixtures has been described in detail on the basis of this special structure of polyvinyl chloride[30-33].

Summarizing, the situation is as follows: along the PVC chain there is a regular sequence of dipoles which in the normal amorphous state do not enter into any stabilizing interactions. Around these more or less free dipoles, local motions can take place, which, *e.g.* in dynamic mechanical experiments, are responsible for the well-known broad secondary relaxation region at temperatures around $-60\,^{\circ}C$ (at 1 Hz), which is typical for PVC. A vinyl chloride homopolymer should not, therefore, strictly speaking be regarded as a single-phase system: there is a physical net-

work with strongly variable network site densities[*]. If a further mixing component of polar character is added to a system of this kind, *e.g.* a modifier, modifier/PVC interactions arise at the expense of the PVC/PVC interactions. This can result in an enhancement or a reduction of the molecular or segment mobility in the PVC chains, and one can observe a decrease or increase in the glass transition temperature. As already mentioned, such PVC systems have been shown by some X-ray studies not to be strictly single-phase[33,35].

If a compatible modifier or plasticizer is added in a *small* quantity to polyvinyl chloride, it will first combine *predominantly with the dipoles not engaged in interactions*. The region around these dipoles before mixing had been preferentially available for local motions and thus constituted an essential prerequisite for the mobility of PVC chains or chain segments. As a result of the development of the first PVC/plasticizer dipole interactions the mobility of the polymer chains is locally restricted; in the dynamic mechanical measurement this leads to the leveling out or to a complete disappearance of the secondary relaxation region. Macroscopically observable consequences of the dipole/dipole relationships when small quantities of plasticizers have been added are an increase of the elasticity modulus and of the tensile strength and a reduction of the elongation at break, *i.e.* there is a decrease in toughness. Although the glass transition is lowered, the hardness and brittleness increase ("antiplasticization"); at plasticizer contents exceeding about 10% the modulus decreases again and the elongation at break increases[38,69].

A characteristic feature of high-molecular modifiers suitable for use as components of soft PVC mixtures with improved low-temperature properties is that the segment mobilities in the polymer chains are very much more pronounced than they are in chains of unmodified polyvinyl chloride. High-molecular modifiers for single-phase PVC alloys with improved heat deflection temperature, on the other hand, exhibit a lower segment mobility at higher temperatures than does polyvinyl chloride. With rising temperature the segment mobility increases less quickly than in polyvinyl chloride. In alloys of this kind polyvinyl chloride can be regarded formally as a "plasticizing modifier" for a mixing component with a higher glass transition temperature[7,66].

3. Synthesis of New Polymer Modifiers

3.1. High-Molecular Aliphatic Polyesters

Already in the 1940's *Biggs et al.*[50,51] were trying to obtain high-molecular aliphatic polyesters with a narrow molecular-weight distribution by fractional precipitation. However, fractional precipitation is unsuitable for the large-scale production of the desired product. Direct synthesis of high-molecular aliphatic polyesters by simple esterifications or transesterifications invariably yields polyesters with a broad distribution of the molecular weight. Azeotrope esterification, as recommended by *Batzer*[52], has so far also proved to be economically inviable for the synthesis of aliphatic polyesters of high molecular weight and narrow molecular weight distribution.

One example of high-molecular aliphatic polyesters with relatively narrow molecular-weight distributions are the polycaprolactones, which are compatible with PVC[53-55]. According to our measurements, however, the desired low-temperature properties cannot be achieved by modifying PVC with polycaprolactones, perhaps because of the latter's pronounced tendency to crystallize.

It should be possible to synthesize other high-molecular polyesters without low-molecular fractions, *i.e.* without fractions with molecular weights below 10^4 to 10^5, by multistage buildup of the chain (Fig. 2).

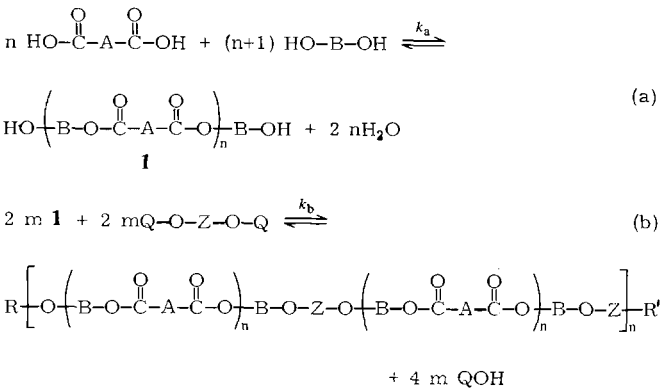


Fig. 2. Scheme of the synthesis for the preparation of aliphatic, high-molecular (polyester)-polycarbonates. (a) Chain buildup by esterification, (b) chain prolongation by transesterification. Q = active group; R, R' = end groups (H or Q); Z = difunctional acyl residue, preferably >C=O.

The most important criterion for useful, difunctional chain extenders suitable for a synthesis of this kind is that the ester groups of the chain extender react with hydroxy groups—*e.g.* by transesterification—whereas the ester linkages of the polymer chain are not allowed to react.

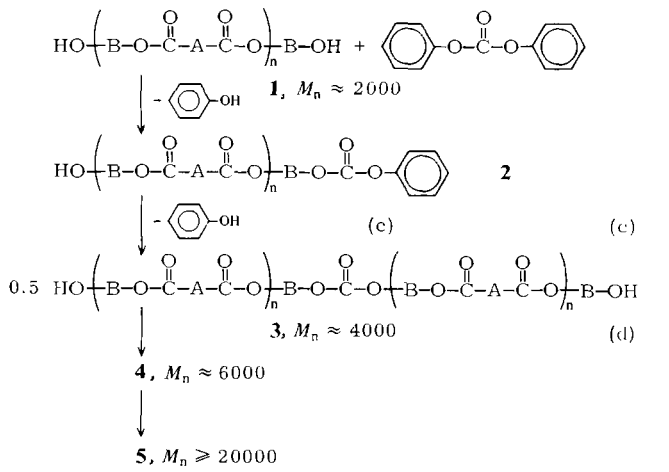
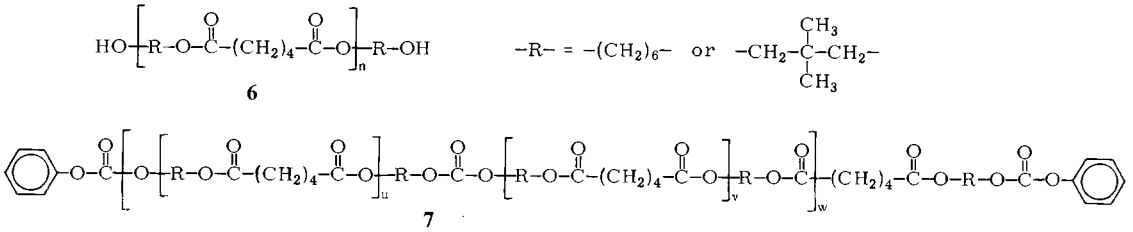


Fig. 3. Scheme of the synthesis for the preparation of (polyester)-polycarbonates. The second prolongation [step (d)] and the further reaction to high-molecular **4** and **5**, in accordance with the first prolongation [step (c)], proceed *via* phenoxycarbonyl-terminated macromolecules. A, B = alkene groups; $n \geq 4$. **1**, **3**, and **4** contain, respectively, about 16, 33, and, 50 ester bonds per macromolecule.

[*] The term network site density denotes the number of physical and chemical cross-linking sites per unit volume of polymer.

Very high-molecular aliphatic (polyester)-polycarbonates[*] can be made by using diaryl carbonates[**] as chain extenders in the presence of basic catalyst and within specific temperature ranges (Fig. 3).

High-molecular, aliphatic (polyester)-polycarbonates can be synthesized in this way without any broadening of the molecular-weight distribution towards low molecular weights. Reaction of aryl esters of aliphatic dicarboxylic acids as chain extenders under these conditions does not lead to corresponding high molecular products. Figure 4 shows the results of some model experiments performed to elucidate the course of the reaction, in which a polyester **6** having a terminal hydroxy group was prepared from adipic acid, hexane-1,6-diol, and neopentanediol ($\overline{M}_n \approx 1700$) and converted into **7** [see also Table 2; formulas **6** and **7** are idealized and presented in schematic form].



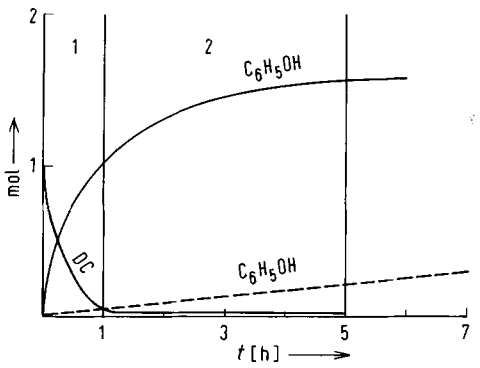


Fig. 4. Course of the polycondensation of diphenyldicarboxylic esters and an OH-terminated polyester **6** from adipic acid, hexane-1,6-diol, and neopentanediol to give (polyester)-polycarbonates **7** at 175 °C; catalyst: 0.0748 g of $NaOC_6H_5$/1000 g of the mixture:

Diphenyl ester + polyester → $2C_6H_5OH$ + (polyester)-polycarbonate
6 **7**

(——) reaction with diphenyl carbonate (DC), (----) reaction with diphenyl sebacate. Step 1: Rapid reaction of diphenyl carbonate to give polyester monoalcohols (cf. **2**); Step 2: condensation to oligomeric (polyester)-polycarbonates (cf. **3**). To achieve quantitative splitting off of the phenol and thus high-molecular (polyester)-polycarbonates, the phenol is distilled off as it forms. Under the same conditions diphenyl sebacate does not form high-molecular (polyester)-polysebacates.

[*] The nomenclature of (polyester)-polycarbonates, *e.g.* from an OH-group-terminated polyester (see **6**, weight-average molecular weight $\overline{M}_w = 2000$), obtained by the esterification of adipic acid with a mixture of hexane-1,6-diol and neopentanediol ["poly(oxycarbonyloxy-hexamethylenoxy-adipoyloxy neopentylene)" see 7], is still unsatisfactory. Some essential structural features, such as the length of the polyester blocks between the carboxylic ester groups, cannot be reproduced in the names.

[**] The particular suitability of diaryl carbonates for the synthesis of polycondensates has long been known (cf. [56, 57]).

As the reaction proceeds the molecular weight increases. Without any further measures being taken, however, only a state of quasiequilibrium is achieved; the average molecular weights $\overline{M}_w$ remain below 15000. For the polycondensation to continue further, it is necessary to remove the phenol formed during the chain-growth process. For example, by distilling off the phenol under vacuum, very high-molecular products ($\overline{M}_w \approx 400000$) can be obtained in relatively short time (4 and 5 h); however, a considerable broadening of the molecular-weight distribution towards higher molecular weights occurs at the same time. The preferred reaction temperatures are in the range 140 to 200 °C. Below about 140 °C the polycondensation slows down sharply with decreasing temperature. Degradation reactions predominate above 200 °C (*e.g.* decarboxylation). On acid catalysis no chain growth was observed.

We found that conversion of aliphatic diols with diphenyl carbonate into high-molecular compounds proceeds largely independently of the diol structure. Besides polyesters with terminal hydroxy groups, appropriate polyethers can also be used. Block copolymers containing both po-

Table 2. Structural parameters of samples of (polyester)-polycarbonate **7**. Reaction: Polycondensation (1 : 1) of diphenyl carbonate and **6** ($\overline{M}_n \approx 2000$) without continuous removal of the phenol by distillation; for the other conditions see Figure 4. Method: combination of gel permeation chromatography (GPC) and viscometry; column combination: Styragels 10^7, 10^6, 10^6, 5×10^5, 10^5, 10^4, 10^3 Å; eluent: $CHCl_3$ at room temperature; detector: refractometer, capillary viscometer. $V_{E,max}$ = elution volume at maximum in gel chromatogram; $U_n = (\overline{M}_w/\overline{M}_n)^{-1}$.

t [h]	$V_{E,max}$ [ct]	$[\eta]_{CHCl_3}$ [dL/g]	$\overline{M}_n$	$\overline{M}_w$	U_n
1	76.6	0.12	1400	2100	0.50
2	75.5	0.15	2200	3000	0.36
3	74.0	0.22	2800	5600	1.00
5	72.9	0.30	4100	9100	1.22
6	72.3	0.33	6700	12400	0.85

Table 3. Some polycarbonates synthesized on a laboratory scale. Molecular weight of the educts: *ca.* 2000. The $[\eta]$-values of the polycarbonates were measured in the specified solvent at 25 °C. THF = tetrahydrofuran. The educts contain two terminal hydroxy groups.

Educts	$[\eta]$-Values of the polycarbonates [dL/g]
Polytetrahydrofuran	≈ 1.1 ($CHCl_3$)
Polyethylene oxide	≈ 0.9 ($CHCl_3$)
Mixtures of polytetrahydrofuran and polybutadiene	≈ 1.0 ($CHCl_3$)
Polyester from adipic acid and diethylene glycol	≈ 1.1 (THF)
Polyester from adipic acid and hexane-1,6-diol	≈ 1.1 (THF)
Mixtures of polybutadiene and polyester **6**	1-2.0 (THF)

lyether and polyester blocks can be produced from mixtures of the two[59].

(Polyester)-polycarbonates **7** (prepared from **6** with $\overline{M}_n \approx 2000$, $[\eta]_{THF} = 1.15$ dL/g), which are particularly suitable for the production of alloys with PVC, have good rubber properties. Their strength (unfilled, green-strength values) is 0.15 MPa; their elongation at break is over 1200% (the corresponding figures for natural rubber are 0.16 MPa and 425%).

Table 3 gives a summary of some (polyester)- and (polyether)-polycarbonates and their block copolycarbonates that have been synthesized on a laboratory scale.

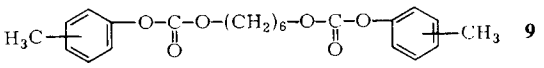
3.2. Tetramethylbisphenol-A Polycarbonate

Tetramethylbisphenol-A polycarbonate (MPC) consists of structural units **8** and can be synthesized from tetramethylbisphenol A and phosgene by interfacial polycondensation[65]. A polycondensation of this kind requires the most quantitative possible acylation of the phenolic hydroxy groups by phosgene or by the chlorocarbonate ester occurring as intermediate during the interfacial polycondensation. Large-scale preparation of MPC proceeds without any problems when the interfacial polycondensation is carried out with high concentrations of the catalyst, at very high pH, and with an excess of phosgene. The four aromatic methyl groups lower the reactivity of the bisphenol component during the polycondensation with acid chlorides, but on the other hand they also endow the tetramethylbisphenol-A polycarbonate with special technical properties, *e.g.* its high resistance to hydrolytic attack and its glass transition temperature of 200—205 °C, about 50 °C higher than that of bisphenol-A polycarbonate (see Table 5, Section 5).

4. Properties of Polymer Alloys of (Polyester)-Polycarbonates and PVC

Adipic diesters with aliphatic monohydric alcohols have long been known as PVC plasticizers[60,64] and, depending on the alcohol, they are reasonably compatible with PVC. Aliphatic polyesters with terminal hydroxy groups and average molecular weights of up to 10000, obtained from diols, *e.g.* hexane-1,6-diol, and adipic or sebacic acid, have likewise been described as usable PVC plasticizers or plasticizing modifiers[61]; the (polyester)-polycarbonates **7** discussed above contain such polyester groups as structural elements.

Aliphatic-aromatic carboxylic esters such as hexamethylenebis(cresyl carbonate) **9** can also be used as plasticizers for PVC[62,63]. Thus, group **10**, the terminal group of the (polyester)-polycarbonates, can solvate the chains of the polyvinyl chloride. On the basis of these structure comparisons extensive solvation of the PVC chains by many



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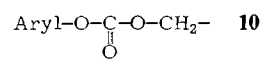

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(polyester)-polycarbonates should be expected. The PVC compatibility of the (polyester)-polycarbonates **7** and of their precursors **6** is shown in Figure 5 by comparing modulus/temperature curves.

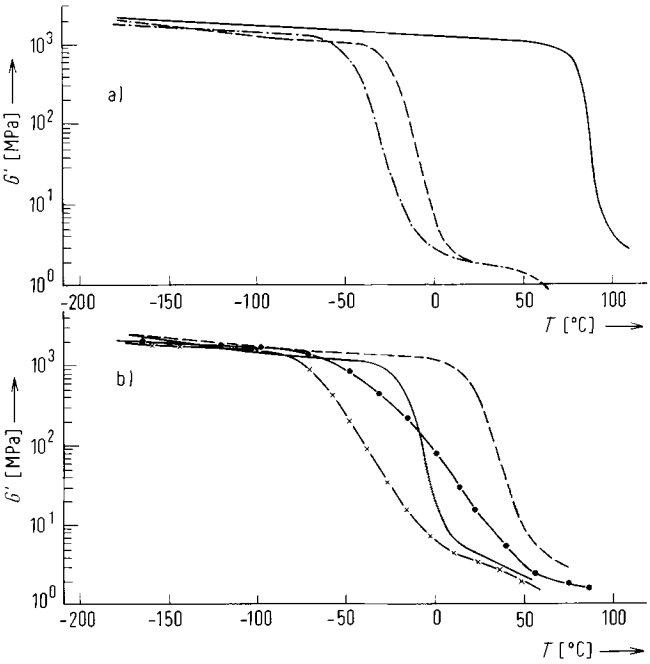

Fig. 5. Modulus/temperature curves of PVC and single-phase PVC alloys or mixtures (figures in wt-%). a) (——) PVC (suspension PVC with a K-value of 70), (----) 50% PVC + 50% polyester **6** ($\overline{M}_n \approx 2000$), (-·-·-) 50% PVC + 50% dioctyl phthalate. b) (——) 50% PVC + 50% (polyester)-polycarbonate **7** (obtained from **6** with $\overline{M}_n \approx 2000$), (----) 75% PVC + 25% **7**, (-•-•-•-) 70% PVC + 30% dioctyl adipate, (-×-×-) 60% PVC + 40% dioctyl adipate.

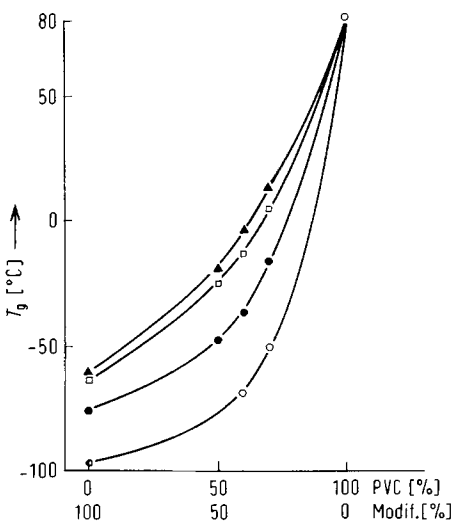

Fig. 6. Comparison of the glass transition temperatures T_g of flexible PVC alloys and mixtures as a function of the PVC content (wt-%), with various plasticizing modifiers (Modif.). (-▲-) PVC + (polyester)-polycarbonate **7** (obtained from **6** with $\overline{M}_n \approx 2000$), (-○-) PVC + dioctyl adipate, (-•-) PVC + dioctyl phthalate, (-□-) PVC + polyester **6** ($\overline{M}_n \approx 2000$).

Figure 6 illustrates the quantitative relationship between the glass point and the composition of several flexible PVC alloys.

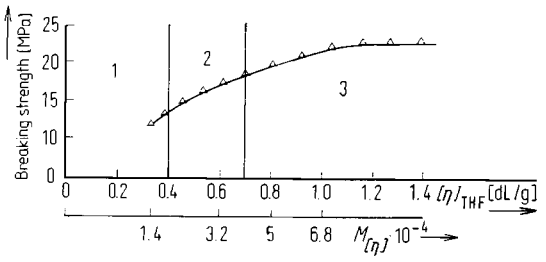

Fig. 7. Relationships between the processability, breaking strength (determined after DIN 53455), and molecular weight or Staudinger index in PVC/(polyester)-polycarbonate alloys; properties of the alloys as a function of the Staudinger index of the (polyester)-polycarbonates **7** (obtained from **6** with $\overline{M}_n \approx 2000$). Regions 1, 2, 3: not processable thermoplastically, moderately processable, and readily processable.

In manufacturing the alloys and by evaluation of samples it was found that the compatible (polyester)-polycarbonates can be particularly well processed with PVC under industrially practicable conditions when the molecular weight $M_{[\eta]}$ of the modifiers is more than 3.5×10^4 (Fig. 7). The characteristic data such as the breaking strength and the elongation at break of these PVC alloys attain a level expected of high-grade flexible PVC alloys only when (polyester)-polycarbonates with high molecular weights are used.

In spite of their high molecular weight, smaller quantities of the (polyester)-polycarbonates **7** are necessary than of other high-molecular modifiers for the production of flexible PVC alloys having a definite Shore hardness (Fig. 8). The migration stability of the (polyester)-polycarbonates **7** in a PVC alloy is illustrated in Table 4.

Table 4. Migration properties of PVC alloys. Migration of plasticizer from PVC alloys made from 60 wt-% PVC (K-value 70) and 40 wt-% modifier into hard PVC and bisphenol-A-polycarbonate (according to DIN 53405).

Modifier	Loss in weight [mg] of soft PVC foils in contact with			
	hard PVC		bisphenol-A-polycarbonate	
	after 24 h	after 12 d	after 24 h	after 12 d
6 ($\overline{M}_n \approx 2000$)	7.1	28.3	2.8	19.3
7 [a]	1.4	6.5	0.5	4.2

[a] **7** (obtained from **6** with $\overline{M}_n \approx 2000$), $[\eta]_{THF} = 1.0$ dL/g

Study of the low-temperature properties of alloys made from PVC and selected (polyester)-polycarbonates yielded the remarkable finding that there are no significant differences between the glass transition temperatures of PVC alloys with polyesters **6** ($\overline{M}_n \approx 2000$) and those with the high-molecular (polyester)-polycarbonates **7**. (Polyester)-polycarbonates of different structures that are compatible with PVC behave in similar fashion.

On the other hand, investigations on the low-temperature fracture behavior of PVC alloys have shown that among the high-molecular, *i.e.* migration-resistant, modifiers tested the (polyester)-polycarbonates **7** occupy a special position (Fig. 9). By using these it is possible to achieve a low-temperature fracture behavior, which is otherwise only obtainable using low-molecular plasticizers of the dioctyl adipate type.

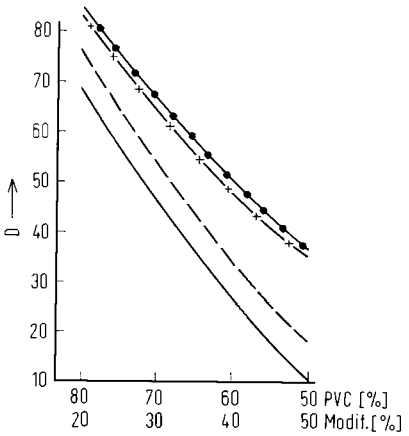

Fig. 8. Shore-D hardness (after DIN 53505) of PVC/(polyester)-polycarbonate alloys and PVC alloys with other modifiers (Modif.). Alloys based on suspension PVC with a K-value of 70; figures in wt-%. (-●-●-●-) (Polyester)-polyurethane (obtained from **6** with $\overline{M}_n \approx 1700$), (-×-×-×-) butadiene/acrylonitrile copolymer with about 30% of acrylonitrile, (----) (polyester-)-polycarbonate **7** (obtained from **6** with $\overline{M}_n \approx 2000$), (——) polyester **6** ($\overline{M}_n \approx 2000$).

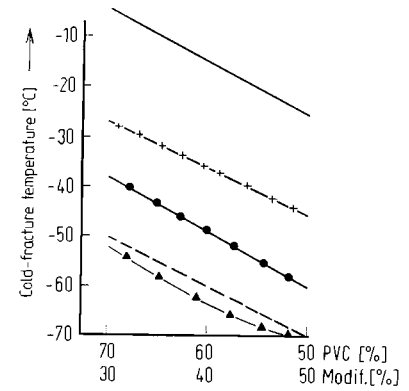

Fig. 9. Cold-fracture temperatures (after DIN 53372) of flexible PVC alloys and mixtures. (-●-●-●-) (Polyester)-polyurethane (obtained from **6** with $\overline{M}_n \approx 1700$), (-×-×-×-) butadiene/acrylonitrile copolymer with about 30 wt-% of acrylonitrile, (----) (polyester)-polycarbonate **7** (obtained from **6** with $\overline{M}_n \approx 2000$), (——) polyester **6** ($\overline{M}_n \approx 2000$), (-►-►-) dioctyl adipate.

The low-temperature behavior is characterized by the temperature range in which, with falling temperature, the failure mechanism changes from ductile to brittle fracture. PVC alloys based on selected (polyester)-polycarbonates accordingly also have a high impact strength below the region of the glass-transition temperature. This was in fact confirmed by plate penetration experiments.

The modulus/temperature variation and the low-temperature behavior provide special information on the mechanical properties of materials as a function of temperature. The shear moduli are measured using relatively low amplitudes, and the low-temperature fracture temperatures using relatively high amplitudes and high loading rates. If we are interested in the rigidity of materials as a function of temperature, the modulus and its abrupt change at the glass transition are the characteristic features; if, on the other hand, we consider the breaking strength as a func-

tion of temperature, then what is decisive is whether the fracture will be brittle or ductile at the temperature in question. The fracture mechanism does not correlate directly with the glass transition of a system; whether a fracture occurs depends on how much force or deformation a system can withstand. In the case of ductile fracture the force or energy necessary to induce failure is very much greater than in the case of a brittle fracture. The force during the breaking process can be measured in a plate-penetrating apparatus (drop weight impact). Information can thus be obtained on the fracture mechanism[70]. Figure 10 shows force/time diagrams from plate-penetrating tests on plates made from various PVC/modifier mixtures and alloys as a function of temperature. For each system there is

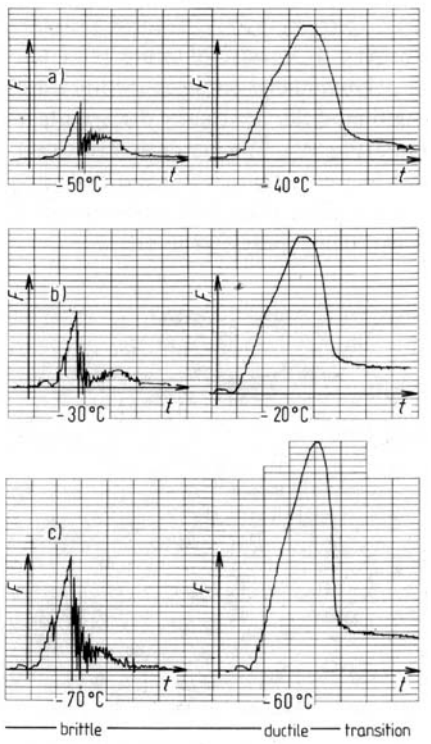

Fig. 10. Results of plate penetrating tests on PVC alloys with a recording dropping-weight apparatus as per DIN 53443: brittle/ductile transition of an alloy from a) 50% PVC + 50% dioctyl phthalate, b) 50% PVC + 50% polyester **6** ($\overline{M}_n \approx 2000$), c) 50% PVC + 50% (polyester)-polycarbonate **7** (obtained from **6** with $\overline{M}_n \approx 2000$).

a temperature range in which a brittle-ductile transition of the fracture behavior occurs under the given conditions. This temperature range can be considered in relation to the glass transition T_g. For the systems in Figures 10a—c the brittle/ductile transition occurs at -50 to $-40\,^{\circ}C$, -30 to $-20\,^{\circ}C$, and -70 to $-60\,^{\circ}C$, respectively; the corresponding T_g values are about -45, -23, and $-20\,^{\circ}C$.

The (polyester)-polycarbonates **7** (Fig. 10c) occupy a special position. The temperature at which the brittle/ductile transition occurs is the most strongly shifted in relation to T_g in the direction of lower temperatures. It remains to be clarified what special structural or morphological features are responsible for this effect.

We favor the following explanation: The PVC mixtures under discussion consist of microphases differing only slightly in composition. The microphases correlate with the fact that wider T_g ranges are found than, for example, in the single-phase "intimately plasticized polyvinyl chlorides"[67,68]. A direct confirmation of a "microphase" morphology of this kind with the aid of dynamic mechanical measurements has so far proved impossible, nor have X-ray small-angle scattering and electron-optical methods yielded any definite evidence.

Any suggestions about the structure and morphology of these systems must be able to account for both the temperature and the molecular-weight variations of the mechanical and elastic properties, *i.e.* for the effect that the temperature difference between the brittle/ductile transition and T_g becomes greater with increasing molecular weight of the (polyester)-polycarbonates **7**.

The following considerations may clarify the findings: the formation of microphases is favored by modifiers of high molecular weight. Even below T_g there are transition ranges of compatibility between the microphases. The effectiveness or stability of physical cross-linking within the microphases and also within the phase boundaries, which determines the mechanical properties of the entire system, depends upon the system's molecular weight and on the temperature.

The average molecular weight of the system (PVC + modifier) is at its lowest when dioctyl adipate is used as the other component, and the resulting poorer properties of the mixtures do not matter because the system has a very low glass-transition temperature.

In the case of the mixtures of PVC and the polyester **6** of $\overline{M}_n \approx 2000$ the average molecular weight of the mixture is higher than when dioctyl adipate is used, high enough to produce microphases. This increase of the molecular weight is, however, insufficient for the generation of a rubbery-elastic state.

In mixtures of PVC and (polyester)-polycarbonates the average molecular weight of the system is so high that a rubber-elastic state can be achieved; in spite of the higher T_g of the system, the physical cross-linking remains active at low temperatures.

Finally, the temperature/toughness characteristics of the mixtures and alloys under discussion here can be determined from these qualitative considerations. It is thus no longer surprising that the aim of improving the low-temperature fracture behavior has been achieved by increasing the molecular weight; it remains worth noting, however, that other properties of practical interest are not impaired by the use of the particularly high-molecular (polyester)-polycarbonates **7** as modifiers.

5. PVC Alloys with Higher Heat Distortion Temperatures

Although the wide range of applications of hard PVC shows that for many purposes the heat deflection temperature of these thermoplastic materials is sufficient, there has been no lack of successful attempts at opening up new fields of application by increasing the deflection stability[7]. The problem is that when the modifier content of PVC mixtures is increased the heat deflection temperature is indeed improved, but there is also an effect on other properties of the system; in many cases the desired aim

can only be achieved by a multicomponent mixture in which the single-phase PVC alloy is but one component. Some thermal and mechanical data for PVC, tetramethylbisphenol-A polycarbonate (MPC), and technical bisphenol-A polycarbonate (PC) are listed in Table 5[65]. What is

Table 5. Characteristics of bisphenol-A polycarbonate (PC), tetramethylbisphenol-A polycarbonate (MPC), and polyvinyl chloride (PVC).

		PVC	MPC	PC
Glass transition temperature (T_g)	[°C]	81	200–205	150
Processing temperature	[°C]	160–220	>260	>260
Refractive index		1.54–1.55	1.546	1.586
E modulus	[MPa]	3000	2400	2200
Tensile strength	[MPa]	65	80	65
Impact strength [a]	[kJ/m²]	[b]	45	[b]
Notch impact strength [a]	[kJ/m²]	2–4	4	>30

[a] At room temperature. [b] Not fractured.

particularly worth noting is the gradation of the glass transition temperatures; given compatibility, the new polycarbonate MPC should prove to be an outstanding modifier. Although the processing temperature of MPC is above 250 °C, this polycarbonate with its glass temperature of 205 °C can be alloyed with PVC. The prerequisite for this is a very good compatibility with PVC at higher temperatures and highly effective thermal stabilization of the system with tin compounds. The transparent alloys[71] (whose production conditions were discovered by *Serini*), exhibit the expected rise of the Vicat softening point (Fig. 11). However, the mixtures are brittle and hence not very useful, despite their very high Vicat grading.

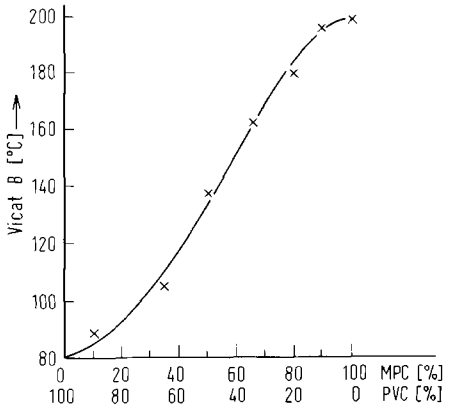

Fig. 11. Vicat B points (after DIN 53460) of alloys made from PVC and tetramethylbisphenol-A polycarbonate (MPC) (data in wt-%).

The method of using an impact-strength modifier active in PVC as an additional alloy component is used successfully in the combination of PVC and tetramethylbisphenol-A polycarbonate. Acrylonitrile-butadiene-styrene (ABS) copolymers, methyl acrylate-butadiene-styrene (MBS) copolymers, and high impact-strength polystyrene (HIPS), *i.e.* polystyrene modified with polybutadiene, are particularly advantageous. Figure 12 shows the relationships of the notch impact strength and the Vicat value as a function of the MPC/HIPS ratio in alloys containing 50% of PVC. In this system increasing quantities of HIPS lead to increasing loss of dimensional stability under heat, but with sufficient notch impact strength Vicat points of over 105 °C can still be achieved; this elevated thermal dimen-

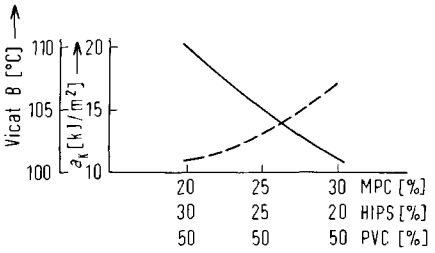

Fig. 12. Relationships between (---) heat deflection according to Vicat B and (——) notch impact strength (a_K, measured as per DIN 53453) in multiphase alloys of polyvinyl chloride (PVC) (suspension PVC with a K-value of 70), tetramethylbisphenol-A polycarbonate (MPC), and rubber-modified polystyrene (HIPS) (figures in wt-%).

sional stability combined with toughness represents a valuable additional advance in the PVC sector.

This alloy from PVC, tetramethylbisphenol-A polycarbonate, and HIPS proves to consist of more than one phase. The spherical polybutadiene particles incorporated with the impact strength modifier are clearly discernible in an electron micrograph (Fig. 13). The matrix is structured. The dark regions are characteristic of PVC and PVC-rich mixed phases. The light regions consist of mixed tetramethylbisphenol-A polycarbonate/polystyrene phases.

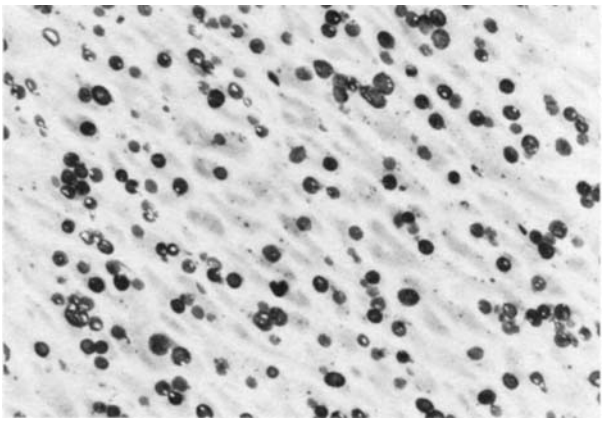

Fig. 13. Transmission electron micrographs (contrasted with OsO_4) of a polymer alloy from 50 wt-% PVC, 25 wt-% tetramethylbisphenol-A polycarbonate (MPC), and 25 wt-% rubber-modified polystyrene (HIPS) (magnification 12500×).

The shear modulus and the loss factor also determine interactions between the components, governed by their mutual solubility (Fig. 14).

The tgδ maximum due to polybutadiene is in the low-temperature region. The PVC peak is somewhat displaced

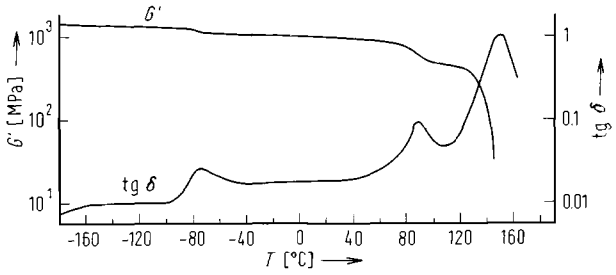

Fig. 14. Modulus/temperature curve of a multiphase polymer alloy from 30 wt-% PVC (suspension PVC with a K-value of 70), 35 wt-% tetramethylbisphenol-A polycarbonate (MPC), and 35 wt-% rubber-modified polystyrene (HIPS). G' = shear modulus, tgδ = loss factor.

in the direction of higher temperatures compared to the peak for pure PVC. No maxima are present for tetramethylbisphenol-A polycarbonate and for polystyrene; evidently these components of the multiphase alloy form a mixed phase, which can be recognized by a glass point of about 140 °C. The electron-optical findings and modulus measurements thus yield the same information about the structure of the alloy.

6. Outlook

In polymer research there is a general increase in interest being taken in single-phase and multiphase polymer alloys and in the development of synthetic plastics in which both these types of polymer alloys are combined with each other.

In the case of single-phase alloys the combination of several polymers frequently leads to new, technically interesting properties, *e.g.* increased or decreased softening points, better workability of thermoplastics, flexibility, or solvent resistance.

In multiphase alloys the generation of disperse polymer phases in a coherent polymer matrix leads to an improvement or removal of the desirable or undesirable properties, respectively, of the matrix (*e.g.* reduction of brittleness and hence increased breaking strength). Advantageous, technically important characteristic properties of the matrix, on the other hand, should not be altered, *e.g.* the softening behavior or workability.

Single-phase or multiphase alloying thus affords various possibilities for varying or adapting the properties of a synthetic plastic to meet more exacting or unusual technical requirements. It is already anticipated that many plastics of the future will be characterized by a combination of disperse phases with single phase multicomponent matrices.

In this review article we have reported on two promising polymers. Tetramethylbisphenol-A polycarbonate (MPC)—a polymer with particular affinities to polymers of other chemical structure—opens up an entry to novel single-phase polyvinyl chloride and polystyrene alloys[65] that display a particularly interesting property profile on additional combination with disperse rubber components.

(Polyester)-polycarbonate—a polymer whose modifying properties are opposite to those of MPC—is an example of a component for the preparation of highly flexible soft PVC alloys that have all the technically useful characteristics of rubber-elasticized multiphase systems at low temperatures.

In our opinion, the historical development of metallic materials and plastic materials shows remarkable parallels: Thus, today, not the pure metals but metal alloys are of major technical interest, so it can be assumed that also in the case of plastics the economic importance of the alloys will surpass that of the chemically individual polymers.

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Liquid Structure and Thermodynamics of Alkane Mixtures

By Andreas Heintz and Rüdiger N. Lichtenthaler*

Spectroscopic investigations and light scattering experiments with saturated, liquid hydrocarbons and their mixtures indicate a specific and distinct influence of the constitution, conformation, and flexibility of the molecule on the structure and macroscopic behavior of such liquids. Orientational order present in pure liquid *n*-alkanes, for example, characteristically affects the thermodynamic mixing properties, such as the enthalpy of mixing ΔH_M and the entropy of mixing ΔS_M, when these liquids are mixed with each other, or with other liquids. Nowadays it is possible to determine thermodynamic mixing properties experimentally with such precision that systematic investigations of these properties allow the behavior of liquids to be studied qualitatively and—with molecular theories of liquids—to some extent also quantitatively. The latest results in this respect, exemplified by mixtures of alkanes, are discussed. These results not only demonstrate the progress made in understanding the relations between molecular (microscopic) and macroscopic properties, but are also of importance for industrial applications (*e.g.* separation processes) in which mixtures of hydrocarbons are involved.

1. Introduction

Saturated hydrocarbons are molecular substances which, in general, are well known. The constitution of an alkane chain is one of the basic fundamentals in teaching structural organic chemistry. As solvents in the laboratory, as widely used raw material for chemical products, and as fuels for the generation of energy, hydrocarbons are of extraordinary importance. The chemical, and above all, the physical properties of these substances in their gaseous and liquid states play a major role in the recovery and refining of crude oil.

Accordingly, to a large extent hydrocarbons and their mixtures are involved in many chemical processes and physical methods in industry (*e.g.* separations). Proper development and economic design of appropriate equipment for these processes is only possible if the chemical and physical properties of the substances to be processed are known. It is, therefore, not surprising that the properties of hydrocarbons have been, and still are collected in comprehensive tabular compilations. Furthermore, many attempts have been made to correlate these data using semiempirical or theoretical approaches. In order to find out, for example, whether a liquid mixture with known composition can be separated into its components by distillation, it is necessary to know the composition of the gaseous phase with which it is in equilibrium. Of course an experiment will reveal the data, but it might be quite expensive and very time consuming. Thermodynamics does not give an answer to this question directly, but defines the conditions of equilibrium. To calculate the compositions of the different phases in equilibrium with one another, however, the chemical constitution of the molecules forming the mixture and the intermolecular interactions between them must be known. Only then does statistical thermodynamics, which connects molecular and macroscopic properties, in principle allow physical properties such as *e.g.* densities, vapor pressures, and phase compositions to be calculated.

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However, at present, the calculation of physical properties is limited to simple, mostly atomic liquids and their mixtures (*e.g.* rare gases and methane). Even for simple, molecular fluids such as, N_2, CO, CO_2, C_2H_2, and H_2O it is still impossible to make quantitatively reliable, theoretical predictions. This is due to the anisotropic shape of these molecules, and intermolecular interactions which, accordingly, are not radially symmetrical, and to additional interactions between multipoles (*e.g.* the dipole of CO, the quadrupole of CO_2) or to hydrogen bonding (*e.g.* H_2O). Recently, however, computer-simulated calculations[1-3] and neutron-scattering experiments[4] have given insight into the relations between molecular structure and macroscopic behavior. Remarkable progress has also been made in the development of statistical theories[5-7]. But the calculation of physical properties using a complete, statistical theory is still not yet possible for "complicated" molecules such as long-chain alkanes, which have many different conformations and have various contributions to their intermolecular interactions. Nevertheless, many helpful methods have been developed, some of which are completely empirical while others are based on statistical models which allow the prediction of important properties such as *P,V,T*-data and phase equilibria.

In this article the latest results of experimental and theoretical investigations which deal with the properties of saturated hydrocarbons are dealt with. In particular, it is shown how new results on the structure of liquids obtained spectroscopically can be incorporated into thermodynamic model theories. In this way it is possible to make consistent predictions of the thermodynamic behavior of alkane mixtures which are important in technical applications. Firstly the behavior of a single molecule will be discussed, *i.e.* of a molecule in the gaseous state at low pressure; the changes which occur in the transition to the liquid state will then be described. Finally, thermodynamic investigations and a molecular theory of alkane mixtures, permitting conclusions with respect to the structure of the liquids will be discussed.

2. The Gaseous State

This section gives a short review of the conformations which a single alkane molecule may adopt. In the final analysis these conformations also determine the intermolecular interactions, and therewith the macroscopic and thermodynamic behavior in the liquid state.

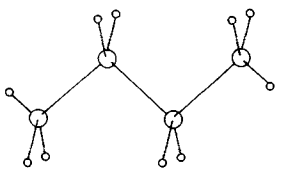

Fig. 1. A possible conformation of *n*-butane.

Figure 1 shows one possible conformation of *n*-butane. It has been established that, on the whole, only "staggered" conformations with a constant C—C—C angle along the chain exist, but that the angle of rotation around the C—C axis may vary. Because of energy restraints, three different angles of rotation are possible, in principle, for each structural unit; one *trans*- (*t*) and two *gauche*-conformations (g^+, g^-). In Figure 2 this is shown schematically for *n*-butane. Because of the strongly repulsive forces between the two methyl groups, the *t*-conformation is energetically more stable than the two *g*-conformations. All intermediate positions are of the *cis*-type, *i.e.* they are not favored energetically because of the repulsion between the CH_3 groups and the H atoms.

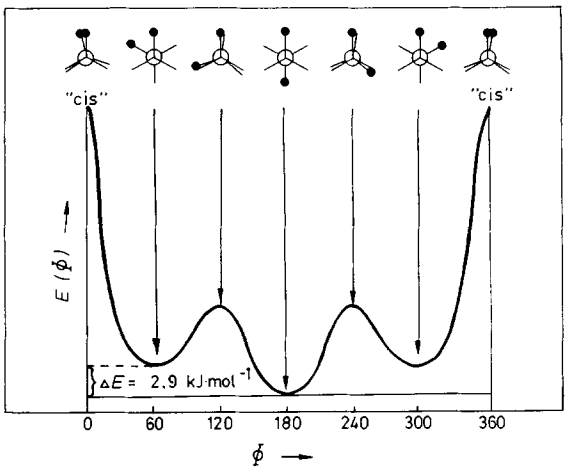

Fig. 2. Potential energy *E* as a function of the angle of rotation Φ of the hindered rotation around the central C—C bond of *n*-butane. 180°: *t*, 60°, 300°: g^+ or g^-; maxima: "*cis*"-conformation.

Put simply, it can be concluded that for an alkane chain different rotational isomers exist having distinct energies differing by $\Delta E(t \rightarrow g^{\pm})$. In case of *n*-butane only three rotational isomers are possible—the *t*-, g^+-, and g^--conformations. Longer chains with n C atoms have n-3 distinguishable structural units which are arranged either in the *t*- or $g^{\pm}$-formation.

If i units are in the g^+- or g^--form, the remaining (n−3−i) units must be in the *t*-form, and the fraction x_i with i $g^{\pm}$-units in the chain is given by [8]:

$$x_i \triangleq m_i \cdot \exp[-i \cdot \Delta E/kT] \qquad (1)$$

In this equation m_i is a weighting factor which accounts for the number of distinguishable distributions of the $g^{\pm}$- and *t*-units within the chain for a given number of *gauche*-units i; *k* is the Boltzmann factor and *T* the absolute temperature. According to *Pitzer*[9] adjacent g^-g^+- or g^+g^--sequences are not possible (steric hindrance) and are hence not included in determining the number m_i in eq. (1). At thermal equilibrium, individual alkane chains are arranged in different conformations, distinguished from one another by internal energies of conformation and molecular shape. The longer the chain, the greater the number of rotational isomers. In general, conformations with many *t*-units bestow a more extended shape to a molecule. In the extreme case when only *t*-units are present, a molecule is a long "zig-zag" rod. Many $g^{\pm}$-units, however, result in a more globular shape. In the gaseous state all these structural isomers exist in equilibrium with one another; their fraction x_i can be calculated from eq. (1) if ΔE is known.

Electron diffraction measurements performed with gaseous alkanes ranging from butane to heptane yield a value of 2.9 ± 0.4 kJ/mol for ΔE[10]. It is important, however, to recognize that for longer chains the energy difference $\Delta E(t \rightarrow g)$ for a structural unit is not completely independent of the arrangement of the other units (t, g^-, g^+). Using the approximation that there is only an effect between structural units located next to one another, *Flory*[11] has developed a matrix method, which is similar to the Ising-model, to calculate conformational equilibria. Up to heptane, exact calculations have been performed[12] for all possible conformations and clearly show a more complicated behavior than that corresponding to Figure 2 and eq. (1), which uses only one parameter ΔE and assumes independent structural units. Nevertheless eq. (1) represents an acceptable approximation for calculating the distribution of rotational isomers.

3. The Liquid State

In practical applications, alkanes are mostly used in the liquid state, and this also, in general, is of greater interest. Usually two cases of the liquid state are distinguished. In one case the alkanes are dissolved in a homogeneous isotropic solvent which consists of simple, approximately spherical molecules (*e.g.* CCl_4 or cyclohexane). The alkane concentration is so small that the molecules do not influence one another, *i.e.* the alkanes are infinitely diluted. In other words the "vacuum" present around an alkane molecule in the gaseous state is replaced by simple solvent molecules. The alkane molecules are kept in solution because of the largely nonspecific, intermolecular interactions with solvent molecules. It is therefore likely that the structural behavior, *i.e.* the equilibrium distribution of the rotational isomers, is essentially the same as in the diluted gaseous state. The other case is the liquid state of pure alkanes or concentrated solutions. Now it is likely that to some extent correlations exist between the alkane molecules because of their asymmetric, chain-like shape and because of the anisotropic intermolecular interactions. Consequently characteristic effects on the structure of the liquids and their thermodynamic properties have to be expected. In particular, it has to be considered to what extend the equilibrium distribution of rotational isomers has been changed compared to that in the gaseous state or in the infinitely diluted solution.

Therefore, those methods which allow the determination of the structure of a single alkane chain at infinite dilution in a simple solvent are firstly described. The extent to which the structure of the chain changes on proceeding to concentrated solutions or pure alkanes is then discussed.

A method widely used to study diluted solutions is the Rayleigh scattering of polarized light. This method is explained in some detail in Figure 3 which shows schematically a single alkane molecule in a momentary, fixed conformation. The incident light has intensity I_0 and wavelength λ, and is polarized in the XY-plane. The scattered light of total intensity I_T is more or less depolarized, *i.e.* the electric vector has amplitudes in the XY- and the XZ-plane. Suitable polarization filters allow the component I_{XZ} of the intensity I_T to be studied separately, *i.e.* the amplitudes of the electric vector of the scattered light in the XZ-plane. I_{XZ} only depends on the differences of the main polarizabilities α_1, α_2, α_3 of the molecule.

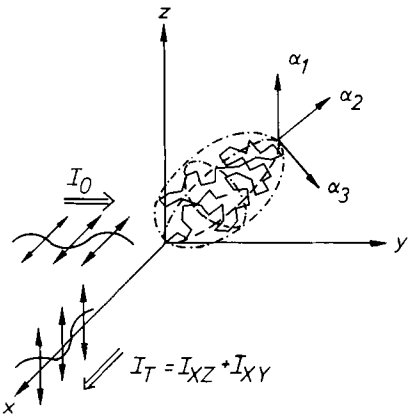

Fig. 3. Scattering of polarized light by a single chain molecule fixed in a momentary conformation (I_0 = incident intensity; I_T = scattered intensity; α_1, α_2, α_3 = main polarizabilities).

The polarizability is defined by the equation $p_i = \alpha_i \cdot E_e$, where p_i is the induced dipole moment in an electromagnetic field of intensity E_e. Optically isotropic molecules with radial symmetry have the same polarizability in all spatial orientations. Optically anisotropic molecules, however, have different polarizabilities α_i in the directions of the three main axis. I_{XZ}, therefore, is a measure of the optical anisotropy and, hence, in general of the anisotropy of the molecular structure. The ellipsoid of polarization enveloping the molecule, as shown in Figure 3, has three main polarizabilities α_1, α_2, α_3 and corresponds to the optical anisotropy of the distinct conformation.

Eq. (2), gives the scattered intensity, and is obtained by averaging all possible orientations of the molecule in space and all possible structures of the rotational isomers[13, 14]:

$$I_{XZ} = \frac{16\pi^4}{\lambda^4} \cdot \rho \cdot I_0 \cdot \frac{1}{15} \gamma^2 \left[\frac{n^2+2}{3}\right]^2 \tag{2}$$

where the molecular optical anisotropy γ^2 is defined by:

$$\gamma^2 = \tfrac{1}{2}[(\alpha_1-\alpha_2)^2 + (\alpha_2-\alpha_3)^2 + (\alpha_3-\alpha_1)^2] \tag{3}$$

In eq. (2), λ is again the wavelength and I_0 the intensity of the incident light *(in vacuo)*, ρ is the particle density of the dissolved molecules which scatter the light, and n is the refractive index of the surrounding medium; n accounts for the effect of the isotropic solvent on the scattered intensity. In order to exclude any effect due to anisotropic contributions from of the solvent, the expression

$$I^*_{XZ}\{(n^2+2)/(n^{*2}+2)\}\{\rho/\rho^*\}$$

has to be subtracted from eq. (2). I^*_{XZ} is the intensity of the corresponding polarized scattered light of the pure solvent, and n^* and ρ^* are its refractive index and density, respectively[15].

The quantitative measure of the anisotropy of a molecule is the molecular optical anisotropy γ^2, which accord-

ing to eq. (3) is the larger the greater the difference between the main polarizabilities of the molecule. Measurements of I_{XZ} yield γ^2 if the other parameters in eq. (2) are known. For a simple molecule like N_2, for example, the two polarizabilities α_1 and α_2 perpendicular to the chemical bond are equal, and the third one, α_3, along the chemical bond is larger ($\alpha_3 > \alpha_1 = \alpha_2$). For a chain molecule like an alkane, however, the α_i-values of each isomeric structure have first to be determined by summation of all the incremental polarizabilities of the C—C and the C—H bonds. The proper average has then to be taken with respect to the equilibrium distribution of all rotational isomers. *Flory*[11] terms this method the "optical valence scheme", which means a theoretical determination of γ^2 is possible, if the following parameters of an alkane chain molecule are known: the angle θ of the C—C—C linkage in the chain, the angle 2ψ of an H—C—H arrangement, the difference ΔE in the energy of the $g^{\pm}$-conformations with respect to the t-conformation, together with the corresponding angle Φ of rotation (compare Fig. 2). Furthermore the differences $\Delta\alpha_{CC}$ and $\Delta\alpha_{CH}$ of the polarizabilities parallel and perpendicular to a C—C and a C—H bond, respectively, must be known. For an alkane chain the following values have been determined: $\theta = 68°$, $\psi = 54.5°$, $\Phi = 120°$, and ΔE 2.9 kJ/mol[14].

The angle θ has been evaluated fairly accurately from electron diffraction measurements on butane to heptane[10]. The values of ψ and Φ are not known with the same accuracy, but it can be shown that small variations in ψ and Φ only influence the theoretical value of γ^2 slightly. On the other hand, the value of γ^2 depends markedly on the values of $\Gamma = (\Delta\alpha_{CC} - 2\Delta\alpha_{CH})$ and of ΔE. Since $\Gamma = 0.54$ Å^3 is a well established value, a fit of the theoretical expression of γ^2 to the experimental values of γ^2 allows ΔE to be determined. It is interesting to note that *Bothorel et al.*[15] obtained best agreement between theoretical and experimental values of γ^2 with $\Delta E = 2.9$ kJ/mol. This is the same result as that obtained from electron diffraction measurements in the gaseous state. This fact confirms the assumption that the conformations of alkanes are essentially the same at infinite dilution in an isotropic solvent like CCl_4 as in the ideal diluted gaseous state.

Now let us turn to the question to what extent the molecular optical anisotropy changes on going from diluted to concentrated solutions or to the pure, liquid alkanes. This problem has been studied extensively by *Bothorel et al.*[15] who performed light scattering experiments with n-alkane/CCl_4 mixtures of various compositions, and used eq. (2) to determine γ^2 in the composition range investigated. Their results are shown in Figure 4. It is obvious that γ^2 increases with increasing alkane concentration. This increase is greater the longer the alkane chain. In principle this behavior could be described by an increase of $\Delta E(t \rightarrow g)$. This would imply that t-conformations are favored energetically because of intermolecular interactions between alkane molecules. The number of t-conformations would have increased relative to the number of the g-conformations, and consequently the molecule should be more extended. Small angle neutron-scattering experiments, however, performed with mixtures of deuterated and protonated alkanes show clearly that the total conformation of an alkane molecule (*e.g. n*-hexadecane) does not change on going from dilute solutions of alkanes in cyclohexane to pure liquid alkanes[16]. Hence the distribution of t- and $g^{\pm}$-sequences within a molecule does not change.

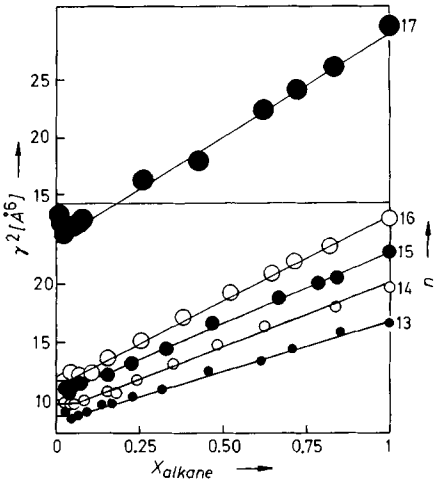

Fig. 4. Molecular optical anisotropy γ^2 of n-alkanes in CCl_4 as a function of mole fraction x [15] (n = number of C atoms).

Accordingly, only very small "ranges of correlation", possibly favoring a parallel orientation of the t-sequences of different molecules with one another, can be responsible for the observed increase in the molecular optical anisotropy. The total shape of a single molecule is not affected. *Kielich*[17] and *Tancrède et al.*[18] have developed a general expression for the average optical anisotropy γ^2_M of a binary mixture, which accounts for the effects of short-range intermolecular interactions:

$$\gamma^2_M = (x_1\gamma^2_{10} + x_2\gamma^2_{20}) + (x_1^2\gamma^2_{10}J_{11} + 2x_1x_2\gamma_{10}\gamma_{20}J_{12} + x_2^2\gamma^2_{20}J_{22}) \quad (4)$$

The contribution to γ^2_M given in the first bracket is due to the different anisotropies γ^2_{10} and γ^2_{20} of the molecules of the two components *1* and *2*, either in the gaseous state or when infinitely diluted in a simple solvent (subscript 0): x_1 and x_2 are the mole fractions of the two components. The term in the second bracket represents the contribution that originates from changes in anisotropy upon mixing because of intermolecular interactions and the correlation of different molecules with one another. J_{ij} is termed the correlation parameter of the molecular optical anisotropy of two molecules i and j. For mixtures of CCl_4 (1) and an n-alkane (2), $\gamma^2_{10} \approx 0$ and $J_{11} = 0$, so eq. (4) reduces to:

$$\gamma^2_M = x_2\gamma^2_{20} + x_2^2\gamma^2_{20}\cdot J_{22} = x_2\gamma^2_{20}(1 + x_2J_{22}) \quad (5)$$

γ^2_M/x_2 corresponds to the optical anisotropy γ^2 represented in Figure 4. The correlation parameter J_{22} of n-alkanes is *ca.* zero up to n-hexane and then increases with increasing chain length. This follows from the dependence of γ^2 on composition, which is linear and increases with $\gamma^2_{20}\cdot J_{22}$ as shown in Figure 4. This increase of optical anisotropy due to segmental, anisotropic interactions between the alkane molecules is called "*C*orrelation of *M*olecular *O*rder" (CMO)[19,20]. CMO occurs particularly with n-alkanes ($n > 6$) and is not observed for corresponding isom-

eric alkanes which are highly branched[21,22]. This is demonstrated in Figure 5 which shows the optical anisotropy γ_{ij} of different isomers of hexadecane, not only at infinite dilution in CCl_4 (γ_{20}^2), but also for the pure alkanes ($\gamma_{22}^2=\gamma_{20}^2(1+J_{22})$; cf. eq. (5) with $x_2=1$). The difference between γ_{20}^2 and γ_{22}^2 increases more and more with decreasing degree of branching on going from 2,2,4,4,6,8,8-heptamethylnonane (i-C_{16}) to n-hexadecane (n-C_{16}). In Figure 5, γ_{ij} is plotted against the ratio $\overline{R^2}/a^2$, where $\overline{R}$ is the average radius of gyration of a molecule and a is the distance between two C atoms.

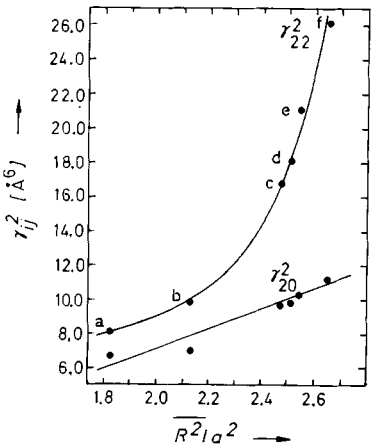

Fig. 5. Molecular optical anisotropy γ_{ij}^2 of isomeric hexadecanes as a function of the ratio $\overline{R^2}/a^2$ ($\overline{R^2}$ = radius of gyration, a = bond length C—C): γ_{20}^2 at infinite dilution in CCl_4; γ_{22}^2 pure hexadecanes. a) 2,2,4,4,6,8,8-heptamethylnonane, b) 6-pentylundecane, c) 6-methylpentadecane, d) 4-methylpentadecane, e) 2-methylpentadecane, f) n-hexadecane [22].

With increasing degree of branching, $\overline{R^2}$ decreases whereas a remains constant, *i.e.* $\overline{R^2}$ is a measure of the geometric anisotropy of the hexadecane molecules, having its largest value for the n-alkane. An increase in $\overline{R^2}$, therefore, is combined with an increase in the optical anisotropy. In fact, at infinite dilution in CCl_4 the corresponding increase of γ_{20}^2 is observed, which is not too marked and nearly linear. $\gamma_{22}^2=\gamma_{20}^2(1+J_{22})$ of the pure alkanes, however, increases considerably more with increasing $\overline{R^2}$, and hence the difference $(\gamma_{22}^2-\gamma_{20}^2)=\gamma_{20}^2\cdot J_{22}$ also increases. This is an immediate effect of the CMO found particularly between the molecules of the non-branched n-alkanes (large values of J_{22}) and only to a small extent between the molecules of highly branched isomers (small values of J_{22}). In the meantime, measurements of the magnetic birefringence performed on n-alkanes dissolved in CCl_4 have clearly confirmed the CMO[23].

IR spectroscopic investigations with liquid n-alkanes and polyethylene carried out by *Snyder*[24] point towards an increased amount of g-conformations at the ends of longer chains of alkanes. Consequently this would imply a change of the conformation of each individual molecule compared to that in the gaseous state or at infinite dilution. Raman spectroscopic investigations[25], however, show no change of the conformation of an alkane chain on going from the pure liquid to infinite dilution in CCl_4. The equilibrium distribution of t- and g-sequences within a molecule is essentially the same in both cases, since the Raman spectra are not altered (cf. also [23]). Only a variation in temperature results in a change in the Raman spectra, *i.e.* the characteristic frequencies and intensities are changed, because of conformational changes. At lower temperatures in the solid state, the alkanes are almost completely arranged parallel to one another, *i.e.* more or less only all-*trans* conformations are present. This has been established from the increased amount of longitudinal acoustic modes in the Raman spectra of all-*trans* n-alkane chains[26,27]. For the liquid state, discussed here, spectroscopic investigations confirm the conclusion already deduced from small angle neutron-scattering experiments: At a given temperature the CMO does not affect the total conformation of a chain, but represents short-range orientational order between a few neighboring chain segments of different molecules.

In general, it is not possible to predict *a priori*, how the CMO affects the macroscopic behavior of n-alkanes. In the following, the effects on the thermodynamic properties of these liquids are mainly discussed.

4. Thermodynamic Investigations

The importance of thermodynamic properties of alkane mixtures in technical applications has already been emphasized. Therefore, the thermodynamic properties of mixing alkane mixtures will now be discussed. A thermodynamic mixing property ΔZ_M of a binary mixture in general is given by:

$$\Delta Z_M = Z_M - x_1 Z_1 - x_2 Z_2 \qquad (6)$$

The property Z may be: the molar enthalpy H, the molar entropy S, the molar volume V, the molar internal energy U, the molar free energy F, or the molar free enthalpy G, *etc.* ΔZ_M is the difference between Z_M of the mixture (index M) and the contributions to Z of the pure components (indices 1 and 2); x_1 and x_2 are the mole fractions. ΔG_M, the free enthalpy of mixing, for example, can be used to determine the chemical potentials μ_1 and μ_2, which must be known for calculations of phase equilibria. As is well known, two phases are in thermodynamic equilibrium with each another, if the chemical potential of any component is the same in both phases.

Figure 6 shows experimental results for the molar enthalpy of mixing (ΔH_M) of some mixtures of n-alkanes and their branched isomers with cyclohexane. These results have been obtained using a new type of flow calorimeter[28,29]. In Figure 7, corresponding experimental data of the molar volume of mixing (ΔV_M) are shown[30], which have been determined from very precise density measurements[30]. It is noticeable on the one hand that ΔH_M and ΔV_M increase with increasing length of the n-alkane chain, and on the other that ΔH_M and ΔV_M are significantly smaller for those mixtures with branched isomers (*e.g.* i-C_{16}) compared to mixtures of the corresponding n-alkanes (*e.g.* n-C_{16}). A similar effect has been observed for the molar entropy of mixing, ΔS_M. The values ΔS_M of various isomeric alkanes mixed with cyclohexane (c-C_6) at equimolar composition are shown in Figure 8 as a function of the

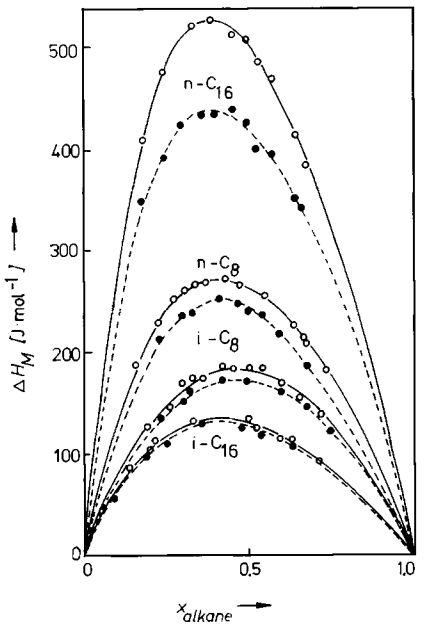

Fig. 6. Experimental molar enthalpy of mixing ΔH_M for mixtures of cyclohexane and isomeric alkanes as a function of the mole fraction x_{alkane} at 298.15 K (—, o) and at 313.15 K (---, •) at 1 bar [28] (i-C_8 = 2,2,4-trimethylpentane).

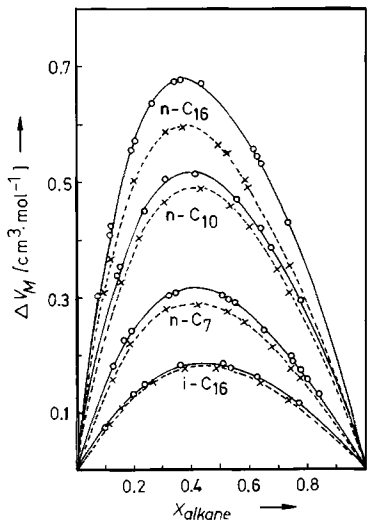

Fig. 7. Experimental molar volume of mixing ΔV_M for mixtures of cyclohexane and isomeric alkanes as a function of the mole fraction x_{alkane} at 298.15 K (—, o) and at 313.15 K (---, ×) [29].

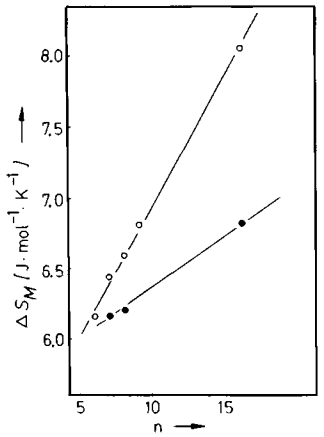

Fig. 8. Experimental molar entropy of mixing ΔS_M for equimolar mixtures of cyclohexane and isomeric alkanes as a function of the number n of C atoms: o n-alkanes, • isomeric alkanes (cf. text) [31].

number of carbon atoms n. It is clear that ΔS_M increases more markedly with n for n-alkanes than for the corresponding branched isomers. The ΔS_M data were obtained from measurements of the vapor pressure of the mixtures[31] from which the molar free energy of mixing (ΔG_M) was initially determined. The Helmholtz relationship $\Delta G_M = \Delta H_M - T\Delta S_M$ immediately yields ΔS_M, since ΔH_M is already known.

Investigations carried out by other groups have produced similar patterns[32-34], confirming a general conclusion, thus: For mixtures of globular molecules, like *e.g.* cyclohexane, CCl_4, or 2,2-dimethylbutane with higher n-alkanes (starting from n-hexane) ΔH_M and ΔS_M increase significantly with chain length, whereas for mixtures with higher branched isomers of these alkanes ΔH_M and ΔS_M are considerably smaller and increase only slightly with the number of C atoms. This effect increases with the degree of branching of the alkane. This is demonstrated in Figure 9[22], for example, with mixtures of 2,2-dimethylbutane and

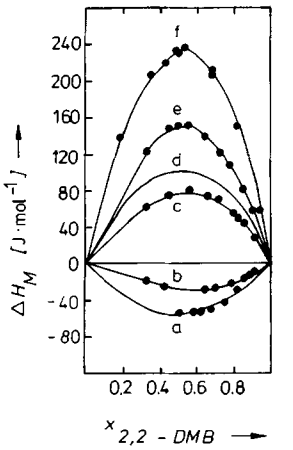

Fig. 9. Experimental molar enthalpy of mixing ΔH_M for mixtures of 2,2-dimethylbutane (2,2-DMB) and isomeric hexadecanes as a function of mole fraction x: a)-f) as in Fig. 5; no experimental data are shown for 4-methylpentadecane [22].

various isomeric hexadecanes: with decreasing degree of branching of the n-alkane, ΔH_M increased markedly extending even from negative to positive values.

It is surprising and important to known how significantly different the thermodynamic properties can be for mixtures of isomeric alkanes with the same solvent. Will it be possible to explain this phenomenon with a molecular, thermodynamic theory, which starts from the intermolecular interactions and structures of the molecules? Are there any correlations between the thermodynamic behavior and those structural changes of the n-alkanes in solution with concentration deduced from light-scattering data?

5. Molecular Theory of Alkane Mixtures

One of the most successful theories of the thermodynamic properties of mixtures of chain-like molecules or, more generally, of molecules differing significantly in shape and size is the one first developed by *Prigogine et*

al.[35], later improved by *Flory et al.*[36-38], and finally presented in a more general form by *Patterson et al.*[39]. It is commonly called the Flory theory and its essential physical principles will be briefly discussed.

The macroscopic volume of a liquid is envisaged to be divided up into single cells, each one occupied by one molecule. This conception is based upon the fact that the structure of a liquid is closely related to that of a solid. For chain-like molecules—linear or branched—each segment of a chain occupies a cell. It is not necessary to exactly define the absolute size of a segment (*e.g.* a —CH_2—CH_2- group). For mixtures of chain molecules (*e.g.* alkanes) with a simple molecule (*e.g.* CCl_4, cyclohexane) Figure 10 gives the corresponding representation of a possible molecular arrangement. The cell model of the liquid state is rather outdated for discussing the behavior of simple molecules and their mixtures. For chain molecules, however, and for flexible, complicated molecules and their mixtures, in general, the modern version of this model still represents the statistical fundamentals of the theoretical calculation of mixing properties[36-39].

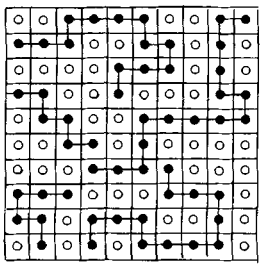

Fig. 10. A "lattice mixture" of chain molecules and simple molecules.

The calculation of thermodynamic behavior usually starts from the free energy F of the pure component or the mixture. For that purpose the following three assumptions are made:

1. Each molecule and each segment have a hard-core volume v^* per cell. The hard cores of the segments of different molecules i and j interact with one another with an attractive potential $-\eta_{ij}/v$, which only extends to the next nearest neighbors of a particular segment; v is the volume of the liquid and the constant of proportionality η_{ij} characterizes the interaction between i and j. In a binary mixture there are three types of such interactions, *i.e.* between segments of molecules of the same kind (η_{11}, η_{22}) and of different kind (η_{12}).
2. The segments of the chain molecules are randomly distributed within the cells, *i.e.* all possible arrangements of the molecules in the mixture are equally probable. It therefore follows that the probability of 1-1 contact with the interaction parameter η_{11} or of 2-2 contact with η_{22} is proportional to the probability of finding two segments of type 1 or 2 neighboring each another, *i.e.* proportional to φ_1^2 or φ_2^2 which are the squares of the probabilities φ_1 or φ_2 of finding a segment of type 1 or 2 in a particular cell. The values of φ_1 and φ_2 are identical with the segment fractions for the two types of molecules:

$$\varphi_1 = \frac{x_1 r_1 v^*}{x_1 r_1 v^* + x_2 r_2 v^*} = 1 - \varphi_2 \tag{7}$$

where x_i is the mole fraction and r_i is the number of segments of a molecule of type i (in the binary case considered here i = 1, 2); $r_i v^*$ is the hard-core volume of one molecule i; the abbreviation

$$V_i^* = r \cdot v^* \tag{8}$$

is used.

3. The third prerequisite concerns the flexibility of the segments within their cells. A single molecule consisting of one segment only ($r_i = 1$) has three degrees of freedom to move around within its cell (translational degrees of freedom). The volume available for unrestrained motion, the free volume v_f, is given by const. $(v^{1/3} - v^{*1/3})^3$. Since the diameter of a segment is proportional to $v^{*1/3}$, the distance between the centers of two neighboring segments is proportional to $v^{1/3}$, and hence the third power of the difference is proportional to v_f. A chain segment does not have three degrees of freedom, as it is chemically bonded to neighboring segments, and thereby is constrained in its motion within its cell. This effect is accounted for by $v_f = \text{const.}(v^{1/3} - v^{*1/3})^{3c}$, where $c < 1$. The smaller the value of c, the more rigid and inflexible is a chain molecule. The general expression for the free energy F_M of a mixture of chain molecules is then given by:

$$\begin{aligned} F_M = &-(A_{11}\eta_{11} + A_{22}\eta_{22} + A_{12}\eta_{12})/v_M \\ &+ T[3kN\bar{r}\bar{c}\ln(v_M^{1/3} - v^{*1/3}) + k\ln W_M] \\ &+ \text{const.} \end{aligned} \tag{9}$$

In the first term, A_{ij} signifies the number of contacts between segments of type i and j in the mixture. Multiplication of these values by η_{ij} and division of the whole term by v_M, the molar volume of the mixture, yield the internal energy U_M of the mixture. The contribution given in the term in square brackets is the entropy S_M of the mixture, corresponding to $F_M = U_M - TS_M$. S_M contains the free volume v_{fM} of the mixture and the number W_M of distinguishable distributions of all chain molecules within all cells: $\bar{r}$ and $\bar{c}$ are the average values of the number of segments per molecule in the mixture, and of the flexibility parameter c of the mixture, respectively. A_{ij}, W_M, $\bar{r}$, and $\bar{c}$ depend on the mole fraction x_i or the segment fraction φ_i of the mixture[37]. The constant "const." contains internal degrees of freedom such as molecular vibrations and depends on the temperature only. In order to calculate the volume v_M of the mixture the known relation $(\partial F/\partial V)_T = P$ (P = pressure) is applied to eq. (9) yielding the thermal equation of state which then can be used to calculate v_M at a given P and T.

For $x_1 = 1$ or $x_1 = 0$ the free energy F of the pure components is obtained from eq. (9) and insertion into eq. (6) gives the following expression[37]:

$$\Delta F_M = \Delta U_M - T\Delta S_M \tag{10}$$

$$\Delta U_M = (V_1^* x_1 + V_2^* x_2)\left\{(\tilde{v}_1^{-1} - \tilde{v}_M^{-1})\varphi_1 P_1^* + (\tilde{v}_2^{-1} - \tilde{v}_M^{-1})\varphi_2 P_2^* + \varphi_1\varphi_2\left(\frac{s_2/s_1}{\varphi_1 + s_2/s_1\varphi_2}\right)\frac{X_{12}}{\tilde{v}_M}\right\} \quad (11)$$

$$\Delta S_M = -k[N_1 \ln\varphi_1 + N_2 \ln\varphi_2] - 3\sum_{i=1}^{2}\frac{N_i V_i^*}{T_i^*}\ln\left(\frac{\tilde{v}_i^{1/3}-1}{\tilde{v}_M^{1/3}-1}\right) \quad (12)$$

$$\Delta V_M = (V_1^* \cdot x_1 + V_2^* x_2)(\tilde{v}_M - \varphi_1\tilde{v}_1 - \varphi_2\tilde{v}_2) \quad (13)$$

$$\Delta H_M = \Delta U_M - P\Delta V_M \quad (14)$$

$$\Delta G_M = \Delta H_M - T\Delta S_M \quad (15)$$

The abbreviation $\tilde{v}_i = v_i/V_i^*$ has been used in eq. (11)—(15). The parameters P_i^* have the dimensions of pressure and are proportional to η_{ii}; the quantities T_i^* have the dimensions of temperature and are defined as:

$$T_i^* = \frac{P_i^* v^*}{k c_i} \quad (16)$$

Another important definition is that of X_{12}:

$$X_{12} = \frac{s_1}{2v^{*2}}(\eta_{11} + \eta_{22} - 2\eta_{12}) \quad (17)$$

The parameters s_i are given as the ratio surface/volume of the hard cores. To some extent they are a measure of the compactness of a molecule.

Without discussing the derivation of these equations, the following general statements can be made: The energy of mixing, ΔU_M, given by eq. (11), is the sum of two contributions. The first term, the interaction-energy term with X_{12} contains the pair-interaction parameter η of the mixture multiplied by $\varphi_1\varphi_2$. This term causes ΔU_M to have the typical, parabolic composition dependence which is in fact observed experimentally. The second term is the equation of state term accounting for the difference of the free volumes of the pure components and the mixture. The second contribution usually is small compared to the first and takes into account the changes of volume upon mixing and the corresponding effects on ΔU_M.

The entropy of mixing also contains two contributions. The first term with $\ln\varphi_i$ is the combinatorial entropy, which takes into account the number of distinguishable distributions of all molecules of the mixture within all cells, reduced by the corresponding number of the pure components. This combinatorial entropy was first derived by *Flory* and *Huggins*[40,41].

The second contribution to ΔS_M is again the equation of state term which contains the logarithmic difference of the free volumes of the mixture and the pure components, and which is usually small compared to the combinatorial contribution.

The enthalpy of mixing ΔH_M differs from ΔU_M only by the additional term $P\Delta V_M$ which is negligible at ambient pressures, but plays a major role at high pressures.

For practical application of these theoretical expressions of the mixing properties it is important that all parameters of the pure components, like V_i^*, c_i, v_i, s_i, and P_i^*, be obtained by fitting the theoretical thermal equation of state to experimental data of the pure components. The thermal expansion coefficient and the compressibility, for example, are suitable for such a fitting procedure. Hence, the theoretical expressions of the mixing properties are already formed "in the trend of the problem" for any particular mixture. X_{12} is the only adjustable parameter. This is one of the reasons for the success of the Flory theory, *i.e.* using only one adjustable parameter (X_{12} to obtain a good representation of the mixing properties for a wide range of mixtures of chain molecules and polymer solutions. As a molecular property the parameter X_{12} must be independent of composition, temperature and pressure.

The significance of successful molecular theories, like the Flory theory just discussed, is given by the fact that thermodynamic mixing properties (*e.g.* ΔG_M), the chemical potentials of each component in a mixture and hence phase equilibria can be calculated knowing just the interaction parameter X_{12}. It is not necessary to have additional experimental data, whose determination usually is very time consuming and quite expensive.

6. Orientational Correlation (CMO) in Alkane Mixtures

To examine the applicability and consistency of the Flory theory values of X_{12} obtained by fitting the theoretical expression of ΔH_M to experimental ΔH_M data will be discussed. Values of X_{12} determined in this way for mixtures of cyclohexane and various alkanes of different chain length and different degree of branching are plotted against the number n of C atoms per molecule in Figure 11[29,32].

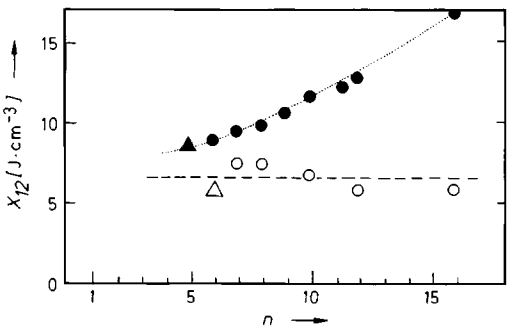

Fig. 11. Parameter X_{12}, determined from the compositional dependence of ΔH_M for mixtures of cyclohexane and isomeric alkanes as a function of the number n of C atoms at 298.15 K; ○, ● [29]; △, ▲ [32]; ●, ▲ *n*-alkanes; ○, △ branched alkanes (see text).

The following branched alkanes were investigated: *i*-C_6: 2,2-dimethylbutane, *i*-C_7: 2,2-dimethylpentane, *i*-C_8: 2,2,4-trimethylpentane, *i*-C_{10}: 2,6-dimethyloctane, *i*-C_{12}: 2,2,4,6,6-pentamethylheptane, *i*-C_{16}: 2,2,4,4,6,8,8-heptamethylnonane.

For mixtures containing *n*-alkanes X_{12} increases significantly with n, whereas it remains practically constant for those mixtures containing the branched alkanes. With short chains (small n) the difference in X_{12} between the two types of mixtures is small.

This result points towards the following discrepancy in the Flory theory: According to eq. (17), X_{12} represents the difference of the segmental interaction parameters η_{ii}.

Therefore, the values of X_{12} should vary only slightly in going from *n*- to branched alkanes. The intermolecular interactions between a methylene group and a CH_3 or $>CH$ group are expected to be fairly similar if the molecules are somewhat arbitrarily distributed in such segmental groups. A molecular interpretation of the results shown in Figure 11, however, would require a distinct difference in the interactions between the different segmental groups, which contradicts all plausible, physical arguments on the different interactions between chemically similar groups[32].

It is, therefore, reasonable to explain these discrepancies of the theory in terms of the molecular orientational correlations present between *n*-alkane molecules previously determined in light-scattering experiments, *i.e.* the parameter X_{12} has to be separated into two parts: one denoted X_{12}^{∞}, is independent of orientation and is the same for mixtures of *n*-alkanes or branched alkanes with cyclohexane, and the other which depends on orientation:

$$X_{12} = X_{12}^{\infty} + X_{12}(\mathrm{CMO}) \tag{18}$$

Comparison of Figure 11 and Figure 5 suggests a direct relationship between the behavior of γ^2 and X_{12}, and this has been formulated empirically[18]:

$$X_{12}(\mathrm{CMO}) = \mathrm{const.}\,\Delta J_{12} \tag{19}$$

where

$$\Delta J_{12} = \tfrac{1}{2}(J_{11} + J_{22}) - J_{12} \tag{20}$$

In case of alkane/cyclohexane (or CCl_4) mixtures $J_{11} = 0$ and hence $\Delta J_{12} = (J_{22}/2) - J_{12}$.

The introduction of CMO forces constitutes an extension of the Flory theory making it possible to rationalize the light-scattering results and the distinct differences in ΔH_M observed for isomeric alkane/cyclohexane mixtures: Upon mixing an *n*-alkane with a globular molecule, like cyclohexane, CCl_4 or 2,2-dimethylbutane, the partial parallel orientation of chain segments favored energetically in pure *n*-alkanes is destroyed. This results in a decrease in the optical anisotropy γ^2 and in an unusually large positive enthalpy of mixing ΔH_M. In comparison, γ^2 changes only slightly, and ΔH_M is much smaller for mixtures of isomeric branched alkanes with cyclohexane (or CCl_4), since there is practically no orientational order to be destroyed during the mixing process.

So far only a few examples of how CMO influences ΔH_M have been presented. This effect has been confirmed by further calorimetric investigations, *e.g.* for mixtures of *n*-alkanes and branched alkanes with tetrabutyltin, a molecule which is also of globular shape[42]. The equimolar ΔH_M is *ca.* 350 J/mol for tetrabutyltin + *n*-hexadecane, whereas for the mixture tetrabutyltin + 2,2,4,4,6,8,8-heptamethylnonane a value of -40 J/mol is observed. This is a significant indication that CMO exists in liquid *n*-hexadecane. Further investigations, confirming the CMO, have been performed with mixtures of squalane (2,6,10,15,19,23-hexamethyltetracosane) and other branched and nonbranched alkanes. Mixtures of branched alkanes with squalane exhibit small, sometimes negative values of ΔH_M, whereas mixtures of *n*-alkanes with squalane clearly exhibit positive, sometimes quite large values of ΔH_M[33]. CMO has been observed even for alkane chains separated by oxygen atoms, *i.e.* dialkyl ethers[43]. Ethylene-propylene copolymers show increasing CMO with increasing amounts of ethylene, *i.e.* with decreasing number of methyl side groups in the main polymer chain[44].

CMO, identified in the first instance by light-scattering experiments, also has a significant effect on the thermodynamic mixing properties. The effects caused by CMO cannot be studied using spectroscopic methods. This clearly shows that very careful investigations of thermodynamic properties are important for a more complete understanding of CMO. In particular, the question arises whether it is possible to give a quantitative description of CMO and consequently whether the influence of CMO on the thermodynamic mixing properties can be calculated.

7. Quantitative Formulation of CMO; Dependence of ΔH_M on Temperature and Pressure

The origin of those forces which are orientationally dependent and cause the CMO probably lie in sterically favored packing phenomena of the *n*-alkane chains which cause the an-isotropic segments to be brought closer to one another, thereby increasing the attractive interaction. In 1979 *Flory* published a semiquantitative theory of the parameter J_{22} characterizing the segmental orientational correlation within alkanes[45]. This theory shows that only steric packing phenomena with a correlation range of about seven segments determine the obtained values of J_{22}. *Vacatello et al.*[46] simulated the CMO using a computer model for liquid *n*-alkanes and found that the CMO has an effect only over short distances, *i.e.* it is limited, more or less, to next nearest neighbors.

With the existance of interactions depending on orientation, an effective dependence of the parameter X_{12} on temperature and pressure has to be expected, which contradicts the assumptions of the original Flory theory. The extension of the theory to take this into account is now discussed *via* the temperature dependence of the mixing properties of mixtures of alkanes and cyclohexane.

For mixtures of *n*-alkanes and cyclohexane, a significant decrease of ΔH_M with increasing temperature has to be expected. The CMO for pure *n*-alkanes is not large at higher temperatures because of thermal motion, and therefore less order is destroyed upon mixing with cyclohexane, *i.e.* less energy has to be supplied during the mixing process. The measure of the dependence of ΔH_M on temperature is the molar heat capacity of mixing:

$$\Delta C_{PM} = \left(\frac{\partial \Delta H_M}{\partial T}\right)_P \tag{21}$$

Negative values of ΔC_{PM} are expected experimentally for *n*-alkane/cyclohexane mixtures. In fact this conclusion is confirmed by the results shown in Figure 12: *n*-C_{16}/*c*-C_6 exhibits strongly negative values of ΔC_{PM}, whereas the values for *i*-C_{16}/*c*-C_6 are small and close to zero, since no CMO is present within the *i*-C_{16}. The data were measured with a Picker micro-flow calorimeter[47,48]. Mixtures con-

taining C_{16} isomers with an intermediate degree of branching fall between these two extreme cases. The curves calculated, using the Flory theory with X_{12} determined from ΔH_M at 25 °C, reproduce the experimental results of *i*-C_{16}/*c*-C_6 in sign and order of magnitude, whereas for *n*-C_{16}/*c*-C_6 values of ΔC_{PM} which are too small are predicted. If the CMO effect is present, the Flory theory fails.

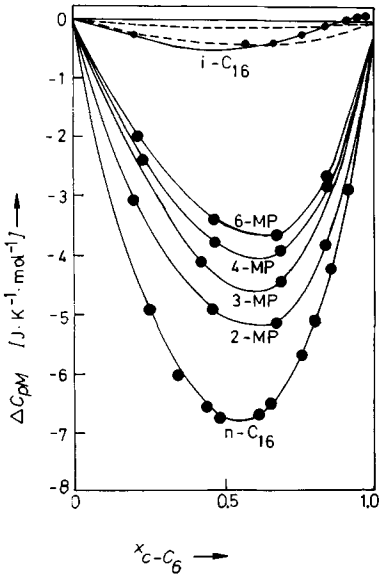

Fig. 12. Experimental molar heat capacity of mixing ΔC_{PM} for mixtures of cyclohexane and isomeric hexadecanes as a function of mole fraction x at 298.15 K; *i*-C_{16} (see text), MP = methylpentadecane; (----) *c*-C_6+*i*-C_{16} (top curve) and *c*-C_6+*n*-C_{16} (bottom curve) calculated with the Flory theory without taking CMO into account [48].

The values of X_{12} determined from ΔH_M data at 25 and 40 °C and given in Table 1 show why: the parameter X_{12} decreases with increasing temperature for the *c*-C_6/*n*-alkane mixtures, whereas it remains practically constant for the *c*-C_6/*c*-C_6 systems. This observation contradicts the Flory theory, which assumes the molecular parameter X_{12} to be independent of temperature.

Table 1. Parameters X_{12} and T_0 at 1 bar.

Mixture	X_{12} (25 °C) [J cm^{-3}]	X_{12} (40 °C) [J cm^{-3}]	T_0 [K]
c-C_6+*n*-C_6	8.8	8.2	180
c-C_6+*n*-C_{10}	11.3	9.8	226
c-C_6+*n*-C_{12}	12.5	10.6	235
c-C_6+*n*-C_{16}	16.5	14.1	232
c-C_6+*i*-C_{10}	6.4	6.2	—
c-C_6+*i*-C_{12}	5.3	5.1	—
c-C_6+*i*-C_{16}	5.2	5.0	—

A recently developed high-pressure flow calorimeter now makes it possible to measure the dependence of ΔH_M of liquid mixtures at pressure up to 600 bar[49–53]. Figure 13 shows results for the system *n*-C_{12}/*c*-C_6. The compositional dependence of the difference ΔH_M(high pressure) − ΔH_M(1 bar) = $\Delta(\Delta H_M)$ is given for several pressures. ΔH_M increases significantly with increasing pressure, namely ≈30 J/mol at the curve maximum for a change in pressure of 300 bar. This is *ca.* 8% of the absolute value of 361 J/mol measured for the equimolar mixture at 1 bar. The theoretical curves calculated with the Flory theory using a constant X_{12} obtained from the measurements at 1 bar predict a completely different dependence on pressure whose sign is wrong for both 180 and 291 bar. Agreement between theory and experiment is only possible when larger values of X_{12} at higher pressures are selected. Table 2 contains values of X_{12} for all systems investigated. The results also indicate that X_{12} is practically independent of pressure for mixtures of branched alkanes with cyclohexane.

Table 2. Parameters X_{12} and T_0 at 298.15 K.

Mixture	X_{12} (1 bar) [J cm^{-3}]	X_{12} (300 bar) [J cm^{-3}]	T_0 (300 bar) [K]
c-C_6+*n*-C_6	8.8	9.5	188
c-C_6+*n*-C_8	9.7	10.7	217
c-C_6+*n*-C_{12}	12.5	14.0	240
c-C_6+*n*-C_{16}	16.5	18.5 [a]	239 [a]
c-C_6+*i*-C_8	7.2	7.2	—
c-C_6+*i*-C_{16}	5.2	5.3 [b]	—
n-C_6+*n*-C_8	0.4	0.4	—
n-C_6+*n*-C_{10}	1.3	1.4	—

[a] Extrapolated from data at 180 bar. [b] Indirectly determined from ΔV_M data in [30].

To overcome these inconsistencies of the theory to predict the dependence on temperature and pressure of the thermodynamic properties of *n*-alkane/cyclohexane mixtures, the CMO has to be incorporated: the following considerations indicate how this can be achieved[52,53]: The motion of the $N \cdot r$ segments of the chain molecule in the liquid state corresponds to $3 \cdot N \cdot r \cdot c$ degrees of freedom ($c < 1$), *i.e.* the liquid is regarded as one containing $N \cdot r \cdot c$ quasi-free segments. Intermolecular forces, which not only depend on the intermolecular separation but also on the relative orientation causing structural order (CMO), act between these quasi-free segments of the *n*-alkanes. The molecular motion is hindered due to orientational correla-

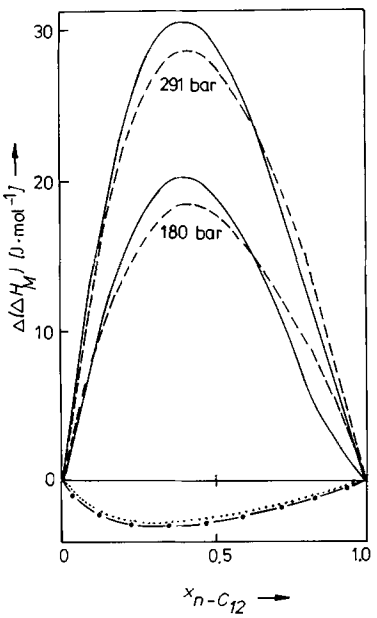

Fig. 13. Effect of pressure on the compositional dependence of ΔH_M for mixtures of cyclohexane and *n*-dodecane. $\Delta(\Delta H_M) = \Delta H_M(P) - \Delta H_M$(1 bar); (—) experimental (---) Flory theory with X_{12} dependent on pressure, (-·-·-) and (·····) Flory theory with X_{12} from 1 bar [52].

tion. The situation is completely analogous to the well-known phenomenon of orientational transitions of simple molecules in the solid state[54]. Figure 14 shows schematically how the particular orientation of an arbitrarily chosen particle (quasi-free segment or single molecule) has an orientational effect on neighboring particles. At larger

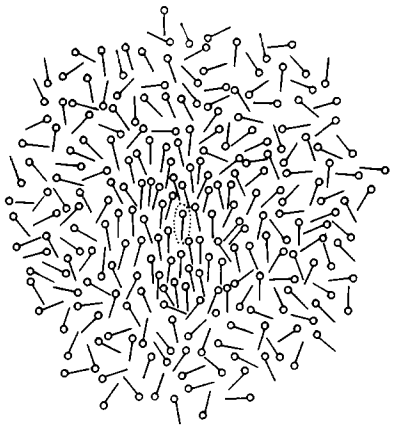

Fig. 14. Symbolic representation of an orientational correlation.

distances there is no correlation between central and remote particles. The range of orientational correlation is therefore limited to a distinct number N^* of neighboring particles which is much smaller than Avogadro's number. At low temperature the orientational order is pronounced; with increasing temperature this is destroyed more and more. Hence the typical character of a cooperative transition is observed where the transition between the more or less ordered state and the completely disordered state occurs within a relative narrow temperature range. Figure 15

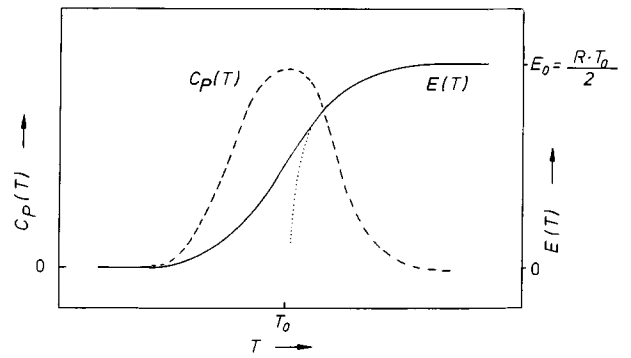

Fig. 15. Schematic representation of the transition energy $E(T)$ and the corresponding molar heat capacity $C_p(T)$ as a function of temperature [52].

shows schematically the temperature dependence of the energy E involved in this transition. E_0 is the total energy necessary to go from the completely ordered to the completely disordered state. The temperature dependence of the corresponding molar heat capacity C_p is also shown. C_p passes through a maximum at the pseudotransition temperature T_0. Above T_0 the dependence of E on temperature can be described as [52–54]:

$$E(T) = \frac{RT_0}{2}\left[1 - \frac{1}{N^*}\frac{T}{T-T_0}\right] \tag{22}$$

The curve from eq. (22) is shown in Figure 15 as the dotted line, and represents the temperature-dependence of the interactions with orientation.

For the chain segments of the *n*-alkanes this signifies that in addition to η_{ii}, an interaction parameter $b_{ii}(T)$—which depends on the orientation and thereby on the temperature must be included. For mixtures of *n*-alkanes with cyclohexane (2) $b_{22} = b_{12} = 0$ since pure liquid cyclohexane, being a globular small molecule, has no structural order. Hence, X_{12} can be formulated as [52,53]:

$$X_{12} = X_{12}^{\infty}\left(\frac{T}{T-T_0}\right) \tag{23}$$

X_{12}^{∞} contains, according to eq. (17), the difference of the η parameters and is independent of temperature and pressure. The second factor in eq. (23) describes the temperature dependence of the interactions containing the pseudotransition temperature T_0. A similar expression has been derived by *Bendler*[55] in a completely different way, by examining the applicability of a theory of structural transitions to the phases of liquid crystals[56].

According to eq. (23), X_{12} decreases with increasing temperature as is expected from the CMO effect and also observed experimentally (cf. Table 1). X_{12} data at different temperatures can be used to determine X_{12}^{∞} and T_0 in eq. (23). For all alkane/cyclohexane systems the values of X_{12}^{∞} are 3–4 J/cm^3, *i.e.* they are fairly constant. This is understandable physically, since X_{12}^{∞} is dependent only on the η-values which are not expected to vary for different alkanes. Values of T_0 are also given in Table 1 and lie in the region of, or slightly below, the melting points of the *n*-alkanes. It is of interest that transitions below the melting point have been observed for *n*-alkanes[57–60].

These considerations with respect to the CMO can be tested with the experimental temperature-dependence of the molecular optical anisotropy. γ_{22}^2 is the optical anisotropy of the pure, liquid alkanes, *i.e.* in this case CMO is present; γ_{20}^2 is the value at infinite dilution in an isotropic solvent, *i.e.* CMO is absent. Assuming X_{12} to be proportional to γ_{22}^2 and X_{12}^{∞} to be proportional to γ_{20}^2, with the same constant of proportionality in both cases, eq. (23) yields:

$$\gamma_{22}^2 = \gamma_{20}^2\left(\frac{T}{T-T_0}\right) \tag{24}$$

This relationship was used by *Dettenmaier et al.*[61] and *E. W. Fischer et al.*[23] to describe the temperature dependence of γ_{22}^2 determined experimentally by light scattering. For *c*-C_6/*n*-C_{12} and *c*-C_6/*n*-C_{16} values of T_0 which agree surprisingly well with the values given in Table 1 were found, thus confirming the temperature-dependent effect of the CMO.

The increase of X_{12} with pressure observed for *n*-alkane/cyclohexane mixtures (cf. Table 2) can be explained using eq. (23). As X_{12}^{∞} is constant, T_0 must increase with pressure if X_{12} increases ($T_0 < T$!). According to eq. (22) E_0, the energy necessary for complete destruction of order within the *n*-alkanes, also increases. This is exactly what is expected, since the higher the pressure, the closer the molecules are packed together, the stronger is the CMO, and the larger is

the transition energy. Table 1 and Table 2 indicate an increase in T_0 of about 8 K per 300 bar for *n*-alkane/cyclohexane mixtures. Orientational transitions observed in the solid state show similar behavior for the pressure-dependence of the transition temperature[59].

Recent Raman spectroscopic investigations at high pressures[62] show a decrease of the all-*trans* conformation and a general decrease of *t*- in favor of *g*-sequences for *n*-alkanes. Consequently, the chain assumes a more globular shape with increasing pressure. This result by no means contradicts the increase of CMO with increasing pressure, since Raman spectra are only affected by changes in the conformation of the total molecule. Changes of short-range intermolecular segmental correlations (*e.g.* the CMO) do not change the Raman spectra.

Eq. (23) is only valid for mixtures of chain molecules exhibiting CMO with small globular molecules without CMO. For mixtures of globular molecules with one another, X_{12} should remain constant. The examples *c*-C_6/CCl_4 and *c*-C_6/*i*-C_8 in Table 2 confirm this conclusion. Also if both components of a mixture exhibit approximately the same CMO, X_{12} should remain constant since the CMO remains constant in the mixture. The CMO effects of both components are mutually compensated (cf. eq. (20) with: $(J_{11}+J_{22})/2=J_{12}$). The values of X_{12} of the mixtures *n*-C_6/*n*-C_8 and *n*-C_6/*n*-C_{10} given in Table 2 reflect this behavior. For all mixtures lying between the extremes of complete destruction or retention of the CMO, it should be possible to derive a general relation for X_{12} by means of the theory developed.

So far the CMO theory has been applied exclusively to ΔH_M. The temperature dependence of X_{12} given by eq. (23) also significantly improves the description of ΔV_M of *n*-alkane/cyclohexane mixtures at various temperatures[30]. The same holds for the description of the entropy of mixing shown in Figure 8. The original Flory theory is only satisfactory for mixtures of branched alkanes with cyclohexane. The prediction of ΔS_M for *n*-alkane mixtures is much better with the CMO model.

The free enthalpy of mixing (ΔG_M) is the same for mixtures of linear or branched alkanes with cyclohexane. The CMO contributions to ΔH_M and $T\Delta S_M$ compensate one another in calculating ΔG_M[31,34]. This effect has also been found for activity coefficients of linear and branched alkanes at infinite dilution in a long-chain alkane with CMO [*e.g.* C_{18}, C_{36}] determined by gas chromatography. The activity coefficients of mixtures containing isomers are practically unchanged, because the CMO effects ΔH_M and ΔS_M producing mutual compensation.

To what extent the quantitative model of the CMO is applicable has not yet been proved. However, at high temperatures and low densities the theory developed is definitely limited, since even the basic assumptions of the Flory theory are only justified for liquid-like densities. Proper extension of the theory to larger temperature and pressure ranges has still to be undertaken.

8. The Effect of Steric Hindrance

For mixtures of long-chain *n*-alkanes with globular molecules like CCl_4, cyclohexane, or 2,2-dimethylbutane a significant contribution of the CMO to the thermodynamic mixing properties must always be expected. The contribution increases with chain length and with decreasing branching of the molecule. However, this order-breaking effect of globular molecules is not always the only additional contribution to ΔH_M and ΔS_M. This is shown by new results for mixtures of *n*-hexadecane with highly branched isomeric nonanes[18,65]. The globular isomers should destroy order in the *n*-C_{16}, and considerably positive ΔH_M and considerably negative ΔC_{pM} are, therefore, expected, by analogy to the mixture *n*-C_{16}/*c*-C_6. The results in Table 3, however, show that quite different, sometimes very low values of ΔH_M are obtained for mixtures of different, but similarly branched nonanes with *n*-hexadecane. For mixtures with *n*-octane the values are even lower, and may be significantly negative. Accordingly, the corresponding values of X_{12} are about zero or negative (*e.g.* $X_{12}=-2.4$ J/cm^3 for 3,3-diethylpentane/*n*-C_8[65]). Again at variance to expectations, ΔC_{pM} is found to be positive for some of these systems (*e.g.* $+0.15$ J·K^{-1}·mol^{-1} for 3,3-diethylpentane/*n*-C_8).

Table 3. Values of ΔH_M [J mol^{-1}] at 298.25 K for equimolar mixtures of *n*-octane or *n*-hexadecane and isomeric nonanes.

	n-C_8	*n*-C_{16}
2,2,4,4-tetramethylpentane	39	236
2,3,3,4-tetramethylpentane	−57	79
2,2,5-trimethylhexane	—	315
3,3-diethylpentane	−83	18

Since the destruction of CMO upon mixing the isomeric nonanes with *n*-alkanes has been detected by light-scattering experiments[18], the positive contribution of the CMO to the mixing properties must, therefore, be compensated by a new mixing effect in these systems. The following may be assumed: Globular molecules like 2,3,3,4-tetramethylpentane and 3,3-diethylpentane are fairly rigid and inflexible for stereochemical reasons. Hence, in the pure liquid a relatively large amount of space between the molecules, which cannot be occupied because of the restricted mobility of segments of these isomeric nonanes, is available. Upon mixing with *n*-C_{16}, the isomeric nonanes destroy the CMO, which consumes energy (positive contributions to ΔH_M and ΔS_M), but at the same time the flexible chains of *n*-C_{16} can occupy the space between the globular nonane molecules, thereby forming new intermolecular contacts, *i.e.* energy "production" (negative contribution to ΔH_M). In comparison to the separated pure components the mixture is closer packed, *i.e.* a higher degree of order is achieved (negative contribution to ΔS_M). For ΔV_M a negative contribution is also expected. The isomeric nonanes 2,2,4,4-tetramethylpentane and 2,2,5-trimethylhexane, however, have a higher flexibility; in the pure liquids less "free" space is available and hence the "steric effect" is not so large compared to the CMO effect upon mixing with *n*-C_{16}. For the corresponding mixtures with *n*-C_8, the CMO effect is not so important as with *n*-C_{16}. Therefore the steric effect, which is the same in both cases, is dominant and causes ΔH_M and X_{12} to be negative.

In general the steric effect will be of secondary importance for small globular molecules which in the liquid are packed so closely to one another that chain molecules cannot penetrate the free space (*e.g.* CCl_4, cyclohexane, 2,2-dimethylbutane). If the globular molecules are large (*e.g.* isomeric nonanes), but still flexible enough to leave no free space (*e.g.* tetrabutyltin), the steric effect is also small. The conclusion that $Sn(Bu)_4$ is rather a flexible, branched chain molecule than a rigid, globular molecule was deduced from the behavior of ΔV_M and ΔH_M of mixtures of this substance with *n*-C_{16} and *i*-C_{16}[30]. Only for large and inflexible globular molecules does the additional steric contribution become effective upon mixing with *n*-alkanes. The steric effect has also been discussed in the interpretation of the thermodynamic mixing properties of polymers (polyethylene, polyisobutylene) dissolved in liquids with large, inflexible molecules like isomeric nonanes and *e.g.* *trans*-decalin[66]. In mixtures of isomeric hexanes and heptanes with *n*-C_{16} and *i*-C_{16} this effect is also of importance[67].

So far, it is not yet clear how this steric effect, in addition to the CMO effect, may be taken into account quantitatively.

9. Conclusions

It has been shown how the large number of different molecular structures, and the macroscopic properties of saturated hydrocarbons and their mixtures can be determined systematically from comprehensive measurements, and how the results obtained can be interpreted. In particular, thermodynamic data of high precision, such as *e.g.* the dependence of the enthalpy of mixing on temperature and pressure, are of great help in developing theoretical concepts for the prediction of macroscopic properties. The Flory theory of mixtures of chain molecules was extended in order to take into account the CMO, a structural ordering effect existing within *n*-alkanes. In this way a more consistent description of the mixing properties of alkane mixtures is now possible. In addition to the CMO a "steric effect" has been observed for some particular types of mixtures which has not yet been incorporated quantitatively into the theory presented.

Recently, *le Noble* and *Kelm*[69] discussed quite extensively the effect of high pressure on chemical reactions in solution. When alkanes are used as solvents it is likely that the pressure dependence of the CMO influences the course of the reaction. Reactions at high pressure might proceed quite differently with an *n*-alkane as solvent (CMO present) than with a strongly branched, isomeric alkane (no CMO exists).

Of course alkanes are a specific group of substances having similar chemical and structural properties, and hence the intermolecular forces acting between the molecules do not vary greatly.

Within other groups of related substances, *e.g.* arenes, or molecules with polar groups, like —OH, —NH_2, and —COOH additional structural and intermolecular effects may occur (formation of hydrogen bonds, molecular complexes, *etc.*), making other theoretical concepts necessary. At present such theories are still not much more than models (see *e.g.* [68]), since the extremely complicated interactions of all molecular properties of large molecules can hardly be developed into a really precise theory which at the same time is easy to handle.

The topics discussed in detail here show, however, that model theories which take into account the essential features of the structure of liquids also give a good description of experimental results. What in particular has to be regarded as essential can only be determined by extensive and systematic investigations using as many methods as possible, *e.g.* spectroscopic and thermodynamic methods. In this respect experimental data for many pure liquid components and mixtures is not available, thus bringing forth a wide field of future research activities.

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COMMUNICATIONS

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

Synthesis and Reactivity of Metal Complexes with the Zwitterionic $Et_3P—CS_2$ Ligand. Structure of the Dithiocarbonato Complex [(triphos)Co(S_2CO)]

By *Claudio Bianchini, Andrea Meli,* and *Annabella Orlandini**

Reaction of triethylphosphane-carbon disulfide ($Et_3P \cdot CS_2$) with cobalt(II) or nickel(II) tetrafluoroborate in the presence of neopentanetriyltris(diphenylphosphane), triphos, and $NaBPh_4$, resulted in formation of the mononuclear complexes **2** and **3**, respectively. In these compounds the zwitterionic ligand $Et_3P—CS_2$ chelates the metal atom *via* both sulfur atoms.

The high reactivity of the ligand $Et_3P—CS_2$ enables the cobalt complex **2** to participate in a variety of reactions.

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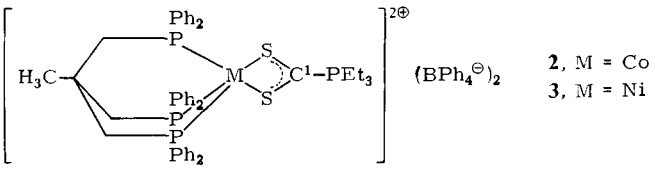
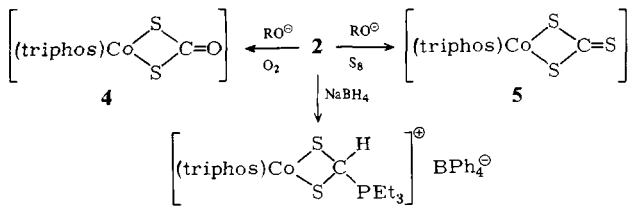


2, M = Co
3, M = Ni

The C^1—P bond can be cleaved by nucleophiles such as alkoxide ions; in the presence of O_2 or S_8, **4** or **5** are formed with the ligands S_2CO^{2-} and S_2CS^{2-}, respectively.



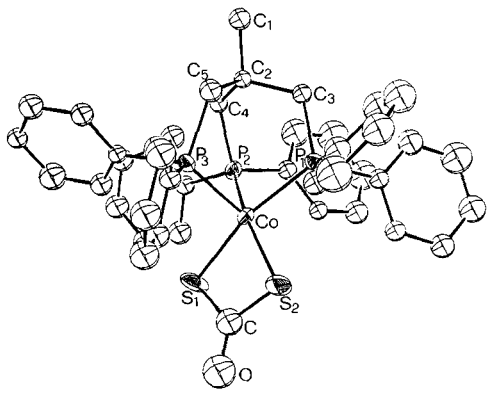


Fig. 1. ORTEP representation of the structure of **4** in the crystal; 50% probability ellipsoids. Important bond lengths [Å] and bond angles [°]: Co—P(1—3) = 2.246—2.271(7), Co—S1 = 2.260(7), Co—S2 = 2.250(6), C—S1 = 1.70(3), C—S2 = 1.69(3), C—O = 1.27(3) Å, S1—Co—P1 = 165.6(3), S2—Co—P2 = 155.5(4), S1—Co—S2 = 75.5(3), S1—C—S2 = 109.1(16), S1—C—O = 124.7(22), S2—C—O = 126.2(21)° [4].

In addition, nucleophiles add to the C^1—P bond; hence **2** and $NaBH_4$ react to give the hydride adduct **6.**

An X-ray structural investigation[4] of **4** (Fig. 1) indicates that the cobalt atom is five-coordinated by the three P atoms of the triphos ligand and by the two S atoms of the S_2CO^{2-} ligand in a distorted square pyramidal environment.

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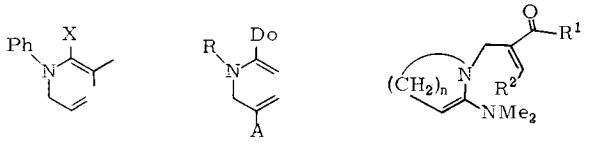
[4] Philips PW 1100 automatic diffractometer. Crystallographic data: $a = 20.294(8)$, $b = 17.954(7)$, $c = 10.218(4)$ Å, orthorhombic, space group $Pn2_1a$, $Z = 4$. The structure was refined from 1065 observed reflections with $I \geq 3\sigma(I)$ to $R = 0.063$ and $R_w = 0.056$, respectively.

Competition between the Aza-Cope Rearrangement and Aldol Addition**

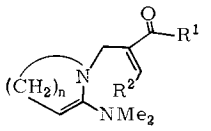
By *Rudolf Gompper** and *Bernhard Kohl*

Aza-Cope rearrangements[1] proceed, in general, at higher temperatures than oxa- and thia-Cope rearrangements. Lewis acids have an accelerating effect[2]. The dialkylamino group, which increases the rate of the oxa-Cope rearrangement[3] has a retarding effect in **1**: **1a** rearranges at 170 °C (cf. [2]), **1b** not until 280 °C[4]. On the basis of results with polar, two-step Cope, and thia-Cope rearrangements[5] it must be expected that the rearrangement will proceed very rapidly with donor-acceptor substituted compounds of type **2.** In fact the dienes **3,** prepared by reacting amidinium salts with sodium hydride, rearrange even at room temperature and *ca.* $10^6 - 10^8$ times as fast as **1b.**



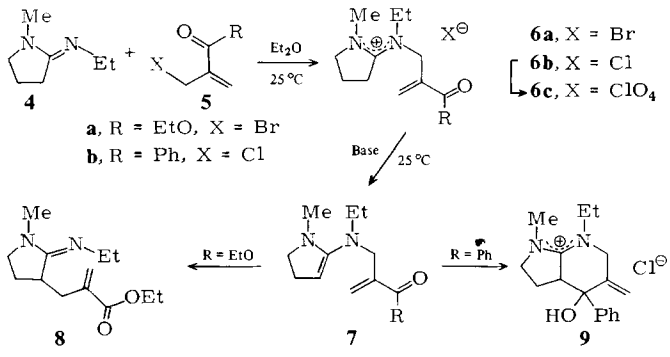
1a, X = H
1b, X = NMe_2

2
Do = Donor
A = Acceptor



3, n = 2, 4

Starting from **4** and **5** we obtained the hygroscopic amidinium salts **6** (**6a**: yield 71%, m.p. = 93—94 °C; **6c**: yield 40%, m.p. = 103—104 °C). Reaction of **6a** with sodium hydride in tetrahydrofuran results in the very rapid formation of the pyrrolidinimine derivative **8** (yield 91%, b.p. = 150 °C/0.01 mbar). Treatment of **6b** with ethyldiisopropylamine in acetone, however, results in formation of the pyrrolopyridine derivative **9** in 79% yield



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[m.p. = 164—166 °C; IR (KBr): 3165, 1668, 1513 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.46$ (t, $J = 7.3$ Hz; 3H), 1.66—2.65 (m; 2H, CH_2—CH_2—N), 3.47 (s; 3H), 3.63—4.15 (m; 5H), 4.53 (s; 2H, CH_2—NEt), 4.75 (s; 1H, =CH_2), 5.20 (s; 1H, =CH_2), 6.45 (s; 1H, OH), 7.20—7.78 (m; 5H)]. Instead of an aza-Cope rearrangement as in **7a,** intramolecular aldol addition occurs in **7b.** This indicates that because of their polarity, donor-acceptor substituents are able to participate directly in the reaction. Aldol reactions and [3,3]sigmatropic rearrangements have similar rates in systems such as **7**; here, orbital symmetry effects do not have an accelerating action.

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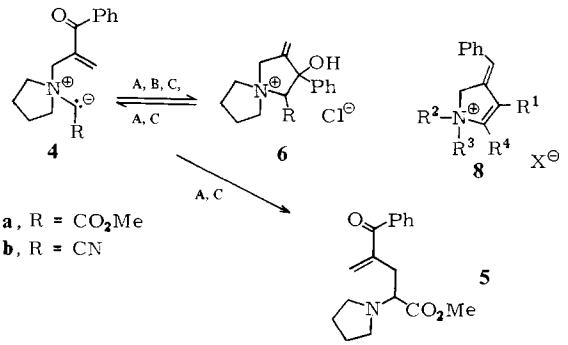
Dipolar Intermediates in the [2,3]Sigmatropic Rearrangement of Ammoniomethanides**

By *Rudolf Gompper** and *Bernhard Kohl*

On the whole, [2,3]sigmatropic rearrangements proceed rapidly even at room temperature (cf. [1]). Apart from the anionic oxa-Cope rearrangement, similarly high reaction rates are observed in [3,3]sigmatropic rearrangements, in general, only if donor-acceptor substituents are present; in such cases, dipolar intermediates are also found[2-4], *i.e.* the rearrangements are two-step. [2,3]Sigmatropic rearrangements of ylides, whereby S_N2' reactions with an anionic nucleophile and a cationic nucleofugic group are involved, can also be categorized in the donor-acceptor scheme. The question therefore arises of whether apart from orbital symmetry, charge effects play a greater role in [2,3]sigmatropic rearrangements than has been previously assumed. The detection of dipolar intermediates would assist in clarifying this matter.



A: NaH, CH_2Cl_2, Δ; B: i-Pr_2NEt, CH_2Cl_2, −10 °C, 1h; C: i-Pr_2NEt, CH_2Cl_2, 25 °C, 20h.

The reactions of the ammoniomethanides **4** indicate that at low temperatures, instead of a [2,3]sigmatropic rearrangement to **5,** an intramolecular aldol addition occurs to give **6** (**6a'**, ClO_4^- instead of Cl^-; m.p. = 214 °C). From differently substituted derivatives we obtained compounds of type **8** *via* **6.** Formation of **6** precedes that of **5**; only **5** (b.p. = 150 °C/0.01 mbar) is formed from **4a** and from **6a** at room temperature.

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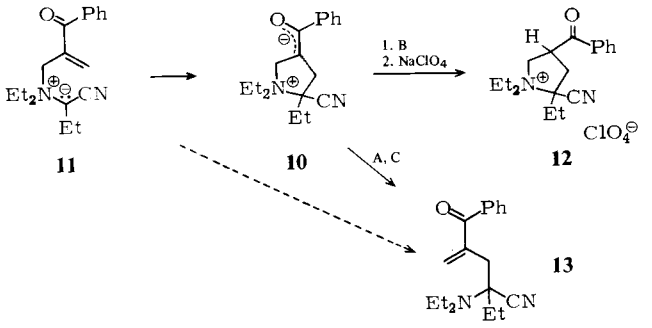
Reaction of α-diethylaminobutyronitrile with α-chloromethylacrylophenone provides the evidence for dipolar intermediates in [2,3]sigmatropic rearrangements. Heating the components in acetonitrile in the presence of ethyldiisopropylamine leads to the rearrangement product **13**. The same reaction in the absence of base yields the pyrrolidinium salt **12**. Formation of **12** and **13** can, therefore, be



A: *i*Pr$_2$NEt, CH_3CN, Δ, 3d; B: CH_3CN, Δ, 5d; C: *i*Pr$_2$NEt, CH_2Cl_2, 25°C, 15h.

explained on the basis that the ylide **11** does not rearrange directly to **13** but forms the dipole **10**, which then, in the absence of ethyldiisopropylamine, is protonated to **12** by acid present in the reaction mixture. That **10** is also an intermediate in the [2,3]sigmatropic rearrangement of **11** to **13** is indicated by the fact that ethyldiisopropylamine completely converts **12** into **13** at room temperature.

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[1] R. W. Hoffmann, *Angew. Chem. 91* (1979) 625; *Angew. Chem. Int. Ed. Engl. 18* (1979) 563.
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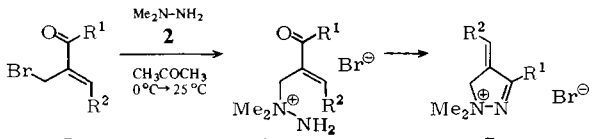
Two-Step Sigmatropic Rearrangement *versus* Aldol Addition of Ammonioimides**

By *Rudolf Gompper** and *Bernhard Kohl*

Ammonioimides liberated by the action of base on 1,1-dialkyl-1-allylhydrazinium salts rapidly rearrange to 1,1-dialkyl-2-allylhydrazines, even at room temperature[1,2]. In 1-acyl-2-allylhydrazinium salts, the [2,3]sigmatropic rearrangement is not observed until 130–150°C[1,3]. Two-step [2,3]sigmatropic rearrangement and intramolecular aldol reactions compete in acceptor substituted ammoniomethanides[4]. How do acceptor-substituted ammonioimides behave?



a, R^1, R^2 = Ph

b, R^1 = Me, R^2 = Ph

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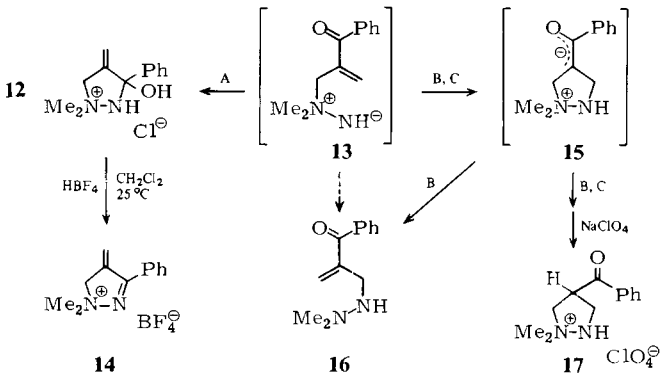
6, formed from **5** and *N,N*-dimethylhydrazine **2** does not react in a [2,3]sigmatropic rearrangement but rather *via* an intramolecular aldol addition to form the 4-benzylidenepyrazolinium salt **7**. When the reaction with **5a** is performed in ether, apart from **7a**, **6a** (decomp. 191–192°C) can be separated by fractional crystallization and be quantitatively converted into **7a** (m.p. = 202°C).

The intermediate appearance of dipolar intermediates **15** in the [2,3]sigmatropic rearrangement of ammonioimides **13** was established in the course of the reaction of α-chloromethylacrylophenone **10** with **2**. In acetone the hydroxypyrazolidinium salt **12** is formed, which gives the methylenepyrazolinium salt **14** (m.p. = 106°C) on reaction with tetrafluoroboric acid. When **10** is heated with **2** in ether, the pyrazolidinium salt **17** (m.p. = 164°C) is obtained after work-up. Its formation arises from protonation of the dipole **15** formed from the ammonioimide **13**. The



A: acetone, −10°C; B: *i*Pr$_2$NEt, Et$_2$O, 25°C; C: Et$_2$O, Δ.

action of **2** on **10** in ether in the presence of ethyldiisopropylamine leads to formation of a 2:3 mixture of **16** and **17**. This finding suggests that **15** is a common intermediate of the formation of **16** and **17**. Since **17** does not react with ethyldiisopropylamine, but is largely decomposed by sodium hydride (thereby only traces of **16** are formed), the mode of formation of **16** *via* **15** has not been completely established.

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Dialkylmagnesium Compounds from Magnesium, Hydrogen, and 1-Alkenes

By *Borislav Bogdanović**, *Manfred Schwickardi*, and *Peter Sikorsky*

We report a two-step synthesis of dialkylmagnesium compounds from Mg, H_2, and 1-alkenes using the recently described method of preparing MgH_2[9].

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$$Mg + H_2 \xrightarrow{cat./THF} MgH_2 \quad (3)$$

$$MgH_2 + 2CH_2{=}CHR \xrightarrow{cat./THF} Mg(CH_2CH_2R)_2 \quad (4)$$

R = H, alkyl

The catalysts for the preparation of MgH_2 (Mg-anthracene-$CrCl_3$ or -$TiCl_4$)[9] are also suitable for the addition of MgH_2 to ethylene or propene to give, respectively, diethyl- or dipropylmagnesium.

Zirconium tetrahalides and magnesium hydride (MgH_2-ZrX_4; X = Cl, Br, I) are considerably more active catalysts for the addition step (4). By this means MgH_2 can also be added smoothly to higher 1-alkenes. The following modification to the procedure has proved useful: Mg is initially hydrogenated to the highly reactive MgH_2 in the presence of the chromium catalyst at room temperature; addition of 1 mol% zirconium tetrahalide at 70—90 °C in the presence of 1-alkenes leads to dialkylmagnesium compounds. The "hydromagnesation" of higher boiling 1-alkenes (b.p. > 70 °C) can be carried out at atmospheric pressure by refluxing (Fig. 1)[12]. The best results are obtained using catalysts containing ZrX_4, particularly ZrI_4 (80—85% conversion after 1—2 h).

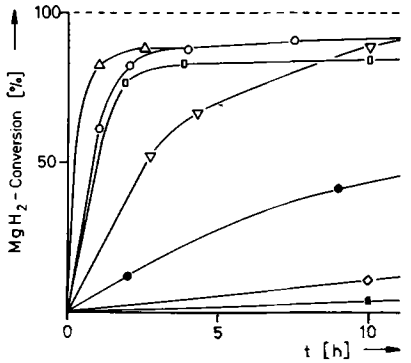

Fig. 1. Course of the MgH_2 addition to 1-octene with time using different catalysts in boiling media; MgH_2 prepared *in situ* at 25 °C in presence of the Cr catalyst. MgH_2 : 1-octene : cat. = 100 : 230 : 1; [cat.] = 0.012 mol/L; (— △ —), ZrI_4; (— ○ —), $ZrCl_4$; (— □ —), $ZrBr_4$; (— ▽ —), $TiCl_4$; (— ● —), $HfCl_4$; (— ◇ —), $(C_5H_5)_2TiCl_2$; (— ■ —), without catalyst.

Reaction of the dialkylmagnesium compounds with electrophiles indicates that the catalytic "hydromagnesation" of 1-alkenes proceeds practically regiospecifically (> 99.7%) in the sense of M→Cl addition. Addition of MgH_2 to 1,1- and 1,2-dialkylalkenes is, in comparison, very slow.

The dialkylmagnesium compounds can be isolated pure and catalyst-free. They can be used *in situ* in syntheses instead of Grignard reagents. For example, tetrabutyltin (83%) could be isolated from a solution containing catalyst, tin tetrachloride, and dibutylmagnesium, or nonanoic acid (78%) could be obtained from dioctylmagnesium with CO_2/H_2O. Trioctylphosphane (84%) and tetraoctyltin (95%) could be prepared, respectively, from pure isolated dioctylmagnesium and phosphorus trichloride and tin tetrachloride, respectively.

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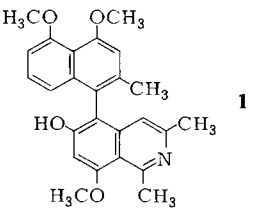
[9] B. Bogdanović, S. Liao, M. Schwickardi, P. Sikorsky, B. Spliethoff, *Angew. Chem. 92* (1980) 845; *Angew. Chem. Int. Ed. Engl. 19* (1980) 818.

[12] 4.0 mL of the suspension was removed at specific intervals, centrifuged, and the Mg content of the clear solution determined acidometrically.

Isoquinolines and Naphthalenes from β-Polyketones: Model Reactions for an Extraordinary Alkaloid Biosynthesis**

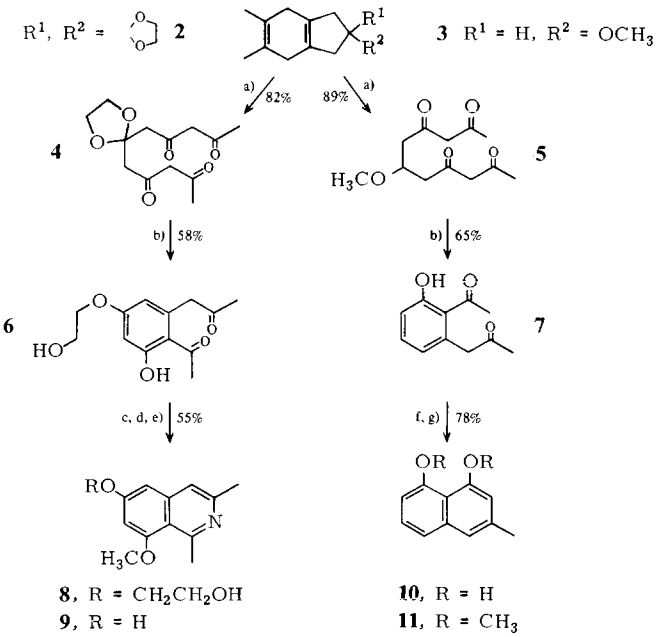
By *Gerhard Bringmann**

Until now it has been assumed that in nature isoquinoline alkaloids are formed, without exception, *via* the Mannich reaction of phenylethylamines with aldehydes or α-oxo acids. Because of its unusual substitution pattern, ancistrocladeine **1**, obtained from the spasmolytically active



1

tropical liana[1] *Ancistrocladus heyneanus*, appears to necessitate a different biosynthetic route. We report the synthetic approach to both molecular moieties (**9** and **11**) of **1** by successive cyclization of β-polyketones, which can be viewed as a model reaction for the formation of an isoquinoline alkaloid from acetate units.



Scheme 1. a) O_3, −78 °C (see *Procedure*). b) SiO_2, Et_2O, 25 °C. c) Me_2SO_4, K_2CO_3, acetone, 25 °C. d) Conc. NH_3, CH_3OH, 25 °C. e) KH, tetrahydrofuran, 25 °C. f) KOH, CH_3OH, 25 °C. g) Me_2SO_4, 10% aqueous KOH, CH_3OH, 12 h reflux.

The synthesis of **9** and **11** is shown in Scheme 1. The ketalized pentaketone **4** [^{1}H-NMR ($CDCl_3$): $\delta = 5.42$, s, olefin. CH of the enol form] is liberated as an oil from **2** by mild ozonolysis in the absence of oxygen. This method of obtaining **4** stems from *Birch et al.*[2], who did not succeed in cyclizing **4** to afford phenols. We found that the ring closure of **4** to **6** (m.p. = 139 °C) can, nevertheless, be realized smoothly by filtering the ozonolysis product through a

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short silica gel column. After methylation of **6**, the second ring closure proceeds smoothly to give the isoquinoline **8** (m.p. = 187 °C), from which **9** (m.p. = 229–231 °C) can be obtained by selective cleavage of the hydroxyethyl group.

11, which also occurs in the free state in tropical ebonies[3], is synthesized from **3**, which like **2** can readily be prepared from 5,6-dimethyl-2-indanone. Mild ozonolysis affords **5**, which immediately cyclizes to **7** (m.p. = 125 °C) on silica gel. The latter compound condenses regiospecifically to the oxidation-sensitive **10**, which also occurs in the anthelmintically active berries of *Diospyros mollis*[4] (m.p. = 141 °C). Methylation leads to the naphthalene derivative **11** (m.p. = 87 °C).

This synthesis of both molecular moieties of **1**, which is orientated towards biogenetic considerations, also opens up an effective route to otherwise difficultly accessible 8-hydroxyisoquinolines.

Procedure

6: **2** (2.82 g, 13.7 mmol) in 1 L of ethanol at −78 °C was treated with oxygen-free ozone. After the apparatus had been flushed with argon, the mixture was hydrogenated immediately at room temperature and atmospheric pressure in the presence of Pd/C. The crude **4** was placed on a short column (silica gel Merck, particle size 0.05–0.2 mm). After 3 h this was eluted with Et_2O/MeOH (95:5). Crystallization from ether yielded **6** (1.65 g, 48%) as small colorless needles.

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$[Fe_6S_9(SCH_2C_6H_5)_2]^{4-}$: A Hexanuclear Iron-Sulfur Cluster Anion Containing the Square-Pyramidal $[(\mu_4\text{-}S)Fe_4]$ Unit**

By *Gerald Henkel, Henry Strasdeit,* and *Bernt Krebs**

Low molecular weight iron-sulfur complexes with tetrahedral coordination of iron are important as model compounds for the active Fe—S centers of non-heme iron proteins[1].

We report the synthesis, properties, and structure of the novel hexanuclear cluster anion $[Fe_6S_9(SCH_2C_6H_5)_2]^{4-}$, obtained by reaction of $[Fe(SCH_2C_6H_5)_3]_n$ with Na_2S_2 and isolated as

$[(C_2H_5)_4N]_4[Fe_6S_9(SCH_2C_6H_5)_2]\cdot H_2O$ **4**

by precipitation with $[(C_2H_5)_4N]Cl$.

The Mössbauer spectrum of **4** at 77 K (source: Rh/Co, zero external magnetic field) exhibits two quadrupole doublets. Accordingly, **4** contains two types of non-equivalent Fe atoms (Fe^a: $\delta = 0.30$, $\Delta E_q = 0.69$ mm/s, Fe^b: $\delta = 0.11$, $\Delta E_q = 0.55$ mm/s, isomer shifts relative to metallic iron).

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The X-ray structure determination of **4** (space group: $P2_1/c$, $a = 1633.9(3)$, $b = 1953.5(4)$, $c = 2172.9(4)$ pm, $\beta = 106.56(3)°$, $Z = 4$, four-circle diffractometer data, $R_1 = 0.060$) shows the presence of discrete $[Fe_6S_9(SCH_2C_6H_5)_2]^{4-}$ ions in the crystal (Fig. 1).

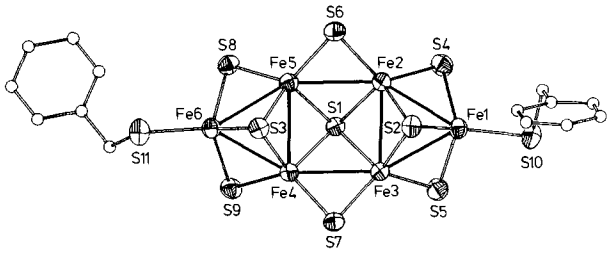

Fig. 1. Structure of $[Fe_6S_9(SCH_2C_6H_5)_2]^{4-}$ in crystals of **4**; vibration ellipsoids of the Fe and S atoms with 50% probability.

In the anion of **4** the six Fe atoms have an approximately planar arrangement (mean deviation from the best plane: 5.8 pm). The Fe_6 core consists of two nearly equilateral coplanar triangles of Fe atoms (∢Fe—Fe—Fe: 59.28(5) to 60.77(5)°, d(Fe—Fe): 269.4(2) to 273.5(2) pm) separated from each other by short Fe—Fe distances (280.4(2) and 274.8(2) pm) to form a square central Fe_4 unit.

A further novel structural principle is the quadruply bridging S1 atom which is located below the center of the Fe_4 square and defines the vertex of an approximately regular square-pyramidal $[(\mu_4\text{-}S)Fe_4]$ unit (mean Fe—S distance: 233.3 pm). In addition, the anion contains inorganic S atoms acting as triply- and doubly-bridging substituents.

The arrangement leads to a distorted tetrahedral coordination of the four central Fe atoms by inorganic S ligands (∢S—Fe—S: 100.32(9) to 124.95(9)°), whereas Fe1 and Fe6 are additionally bonded to one S atom of a benzylthiolate ligand (mean Fe—S distance: 228.4 pm, ∢S—Fe—S: 101.49(9) to 116.36(9)°).

The mean oxidation state of Fe is formally +2.67. Due to the short Fe—Fe distances, which indicate direct metal-metal interactions, assignment of discrete oxidation levels to the central and outer Fe atoms would result in an unsatisfactory description of the true electronic situation. According to the Mössbauer spectrum the two outer Fe atoms are presumably in a higher oxidation state.

The cyclic voltammogram of **4** (0.10 M tetraethylammonium perchlorate in acetonitrile) shows a reduction peak at −0.61 V and oxidation peaks at −0.36 and +0.40 V (relative to Ag/AgCl, scan rate 100 mV/s).

The electronic spectrum of a solution of **4** in acetonitrile shows two peaks at 296 and 329 nm of approximately equal intensities, as well as a shoulder at *ca.* 425 nm[11].

4 could serve as a starting point for the synthesis of a new class of tetrahedrally coordinated Fe—S cluster compounds. The closed parent compound of this class consists of a completely bonded metal cube defined by eight Fe atoms, having six μ_4-S ligands centered above each of its planes. The tetrahedral coordination of each Fe atom is achieved by organo-S ligands.

The central $[Fe_4S_9]$ unit of **4** can be regarded as a fragment of this $[Fe_8S_{14}]$ cage structure.

The $[Fe_7MoS_6]$ unit, which can formally be derived from the $[Fe_8S_{14}]$ cage by substituting one Fe atom of the $[Fe_8S_6]$ core is of particular interest as a model for the active site of the FeMo-protein of nitrogenase and of the isolated FeMo cofactor[6].

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Fe_7MoS_6 has a Fe : Mo : S* (S*: inorganic sulfur) ratio of 7 : 1 : 6, in good agreement with the composition of 7–8 : 1 : 6 determined analytically for the FeMo cofactor of *Azotobacter vinelandii*[6, 9].

EXAFS investigations[10] indicate that molybdenum in nitrogenase and in the FeMo cofactor has two to three iron neighbors ($d = 272$ pm) and three to four sulfur neighbors ($d = 236$ pm). These data are consistent with the coordination of molybdenum in a $[Fe_7MoS_6]$ cube structure.

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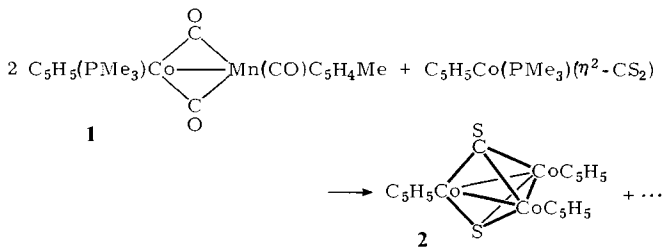
[11] Note added in proof: An analogous complex, obtained by a different procedure, has recently been described [G. Christou, R. H. Holm, M. Sabat, J. A. Ibers, *J. Am. Chem. Soc. 103* (1981) 6269].

$(C_5H_5)_3CoMn_2(CO)_4(CS)PMe_3$ — A Hetero-Trinuclear Complex with a μ_2-*C*,η^1-*S* Bonded Thiocarbonyl Group**

By *Oswald Kolb* and *Helmut Werner**

Recently we reported the synthesis of the first complex containing a μ_3-CS bridge which was obtained from **1** and $C_5H_5Co(PMe_3)(\eta^2\text{-}CS_2)$[1a], and characterized by crystal structure analysis[1b].



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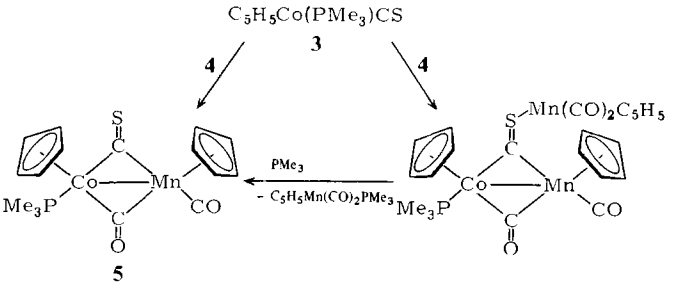
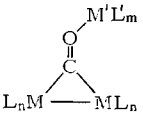
The (Co—Mn) compound **1**, which serves as the synthetic building block for **2**, is advantageously prepared from $C_5H_5Co(PMe_3)CO$ and $MeC_5H_4Mn(CO)_2(THF)$[2]. By means of the analogous reaction of the thiocarbonyl complex $C_5H_5Co(PMe_3)CS$ **3**[3] with $C_5H_5Mn(CO)_2(THF)$ **4** in tetrahydrofuran (25 °C, 24 h), the heterodinuclear complex **5**, in which both metal atoms are bridged by a CO- and a CS-group, [^{1}H-NMR in C_6D_6: $\delta = 4.60$ (C_5H_5Co; d; $J_{PH} = 0.8$ Hz), 4.56 (C_5H_5Mn; s), 0.80 (PMe_3; d, $J_{PH} = 10.0$ Hz); IR: $\nu(CO) = 1912$, 1777 cm^{-1} (in THF); $\nu(CS) = 1106$ cm^{-1} (in Nujol)], is formed. When the starting materials **3** and **4** are used in the molar ratio 1 : 1, in addition to **5** a small amount (*ca.* 5%) of the trinuclear complex **6** is formed, which according to the elemental analysis and mass spectrum [molecular ion m/z 596; additional fragments such as $\mathbf{5}^+$, $C_5H_5Mn(CO)_2CS^+$, and $C_5H_5CoPMe_3^+$] contains one cobalt and two manganese atoms; this product is obtained almost quantitatively by reacting **3** and **4** in the molar ratio 1 : 2.



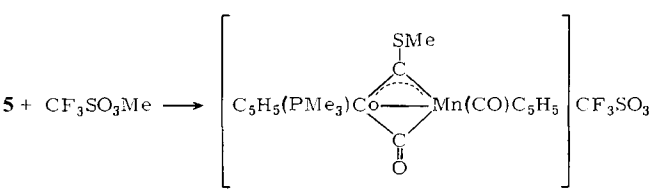
5

The proposed structure for **6** is based on the NMR and IR spectra [^{1}H-NMR in C_6H_6: $\delta = 4.80$ (C_5H_5MnS; s), 4.55 (C_5H_5Mn; s), 4.40 (C_5H_5Co; d, $J_{PH} = 0.7$ Hz), 0.65 (PMe_3; d, $J_{PH} = 10.2$ Hz); IR: $\nu(CO) = 1950$, 1913, 1855, 1800 cm^{-1} (in CS_2); $\nu(CS) = 1050$ cm^{-1} (in Nujol)] as well as on the result of the reaction with PMe_3 (C_6H_6, 60 °C, 40 h) which produces **5** and $C_5H_5Mn(CO)_2PMe_3$, exclusively. Cleavage of the μ_2-CX bridges (X = O, S) in **5** does not occur under these conditions.

A triply bridging function (μ_2-*C*,η^1-*S*), as exhibited by the thiocarbonyl ligand in **6** towards three transition metal atoms, is not known for the CO group. *Shriver et al.*[4] found that strong Lewis acids such as BF_3 or $AlEt_3$ are able to add to the oxygen atom of the μ_2-CO bridges in $(C_5H_5)_2M_2(CO)_4$ (M = Fe, Ru); the electrophilicity of corresponding transition-metal species such as $C_5H_5Mn(CO)_2$ or $Cr(CO)_5$ does not appear to be sufficient for additional coordination to a μ_2-CO group of this type. Reaction of $(C_5H_5)_2Fe_2(CO)_3CS$, which is comparable with $(C_5H_5)_2Fe_2(CO)_4$, with $HgCl_2$ or $[C_5H_5Fe(CO)_2(THF)]^+$ led to isolation of the corresponding 1 : 1 adducts, which presumably have analogous structures to **6**[5].



The high nucleophilicity of the sulfur atom of the thiocarbonyl bridge in **5** is evident, not only in the addition of $C_5H_5Me(CO)_2$ but also in the very rapid and quantitative methylation with CF_3SO_3Me (C_6H_6, 25 °C, 5 min). The spectroscopic data of complex **7**, which contains a bridging methylthiocarbyne ligand, are consistent with the proposed structure [^{1}H-NMR in [D$_6$]acetone: $\delta = 5.52$ (C_5H_5Co; d, $J_{PH} = 0.8$ Hz), 5.43 (C_5H_5Mn; s), 3.50 (SMe; d, $J_{PH} = 0.5$ Hz), 1.37 (PMe_3; d, $J_{PH} = 11.1$ Hz); IR: $\nu(CO) = 1968$, 1833 cm^{-1} (in KBr)].



7

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A Facile, Generally Applicable Synthesis of *N*-Acetyldehydro-α-amino Acids

By *Franz Effenberger** and *Thomas Beisswenger*

Dehydroamino acids are used as educts for the synthesis of α-amino acids. Thus, a series of amino acids could be prepared *e.g.* by addition of acidic compounds such as malonic acid derivatives, indole, imidazole, and thiols to dehydroamino acids[1]. Of particular synthetic significance is the enantioselective hydrogenation of *N*-acyldehydroamino acids or -amino acid esters in the presence of optically active metal complexes as catalysts which produce, respectively, amino acids or amino acid esters in very high optical yield[2].

Until now the known syntheses of dehydroamino acids are either involved, not generally applicable, or rely upon amino acids as starting materials[1].

The recently postulated intermediary 2-iminopropionic acid ester was trapped, by careful acylation, as the *N*-acetyldehydroalanine ester in the alkoxide-catalyzed preparation of pyruvic acid ester from 2-azidopropionic acid ester[3].

We have now obtained *N*-acetyl-**2** and/or *N,N*-diacetyldehydro-α-amino acid esters **3** by warming the 2-azidocarboxylic acid esters **1** in acetic anhydride or acetic anhydride/acetic acid in presence of catalytic amounts of rhenium heptasulfide (Table 1). The azidocarboxylic acid esters **1** are almost quantitatively accessible from the corresponding α-halogen derivatives *via* azide exchange by a phase-transfer reaction with Aliquat 336 as catalyst. Exclusive formation of **2** can be achieved using a smaller Ac_2O/AcOH ratio, advantageously in presence of HCl. Work-up

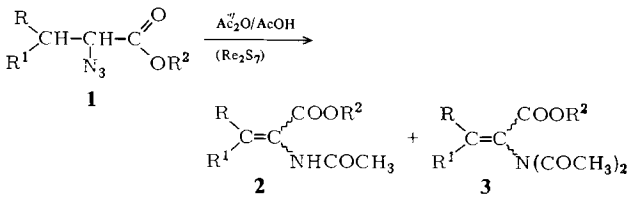

Table 1. *N*-Acetyl-**2** and *N,N*-diacetyldehydroamino acid esters **3** from 2-azidocarboxylic acid esters **1**. Solv. = solvent. A: in Ac_2O, B: in Ac_2O/AcOH (3/7), C: in Ac_2O/AcOH (2/3)/HCl, D: in Ac_2O/AcOH (1/1), E: in Ac_2O/AcOH (1/4)/HCl.

	1				Yield [%]		
	R	R^1	R^2	Solv.	**2** + **3**	Solv.	**2**
a	H	H	Me	A	39 + 40	B	71
b	H	*n*-Pr	Me	A	20 + 75	C	91
c	H	Ph	Et	D	33 + 57	E	90
d	Me	Me	Me	A	93	C	90
e	H	PhS	Me			C	77

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of the **2**+**3** mixture with water is even more favorable (practically no loss of yield).

Z/*E*-Isomeric mixtures of **2**, R^1 = H, R ≠ H, can be quantitatively converted with hydrogen chloride in ether[1] into the *Z*-isomers suitable for the enantioselective hydrogenation[2]. The alkaline saponification of **2** also proceeds smoothly and in high yield to give *N*-acetyldehydroamino acids[4].

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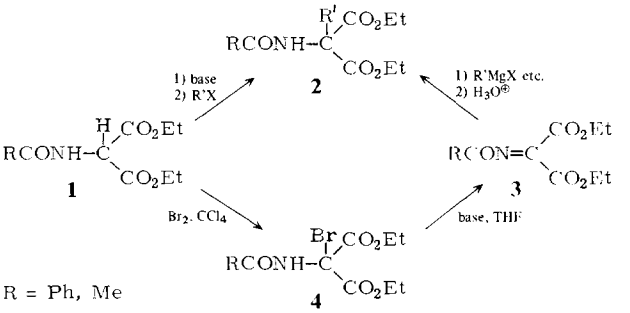
Reaction of Acyliminomalonic Esters with *C*-Nucleophiles, an Umpolung in the Acylaminomalonic Ester Synthesis of α-Amino Acids

By *Reiner Kober, Willi Hammes,* and *Wolfgang Steglich**

In the synthesis of α-amino acids after *Sörensen*[1], the alkylation of an acylaminomalonic ester (**1**→**2**) is the decisive step. We have now found that substitution products of this type can also be prepared by addition of organometallic compounds and other *C*-nucleophiles to acyliminomalonic esters **3**[2].



The bromoesters **4**, accessible in 80–88% yield by bromination of acylaminomalonic esters, have proved suitable precursors for **3**. The action of Hünig's base on *e.g.* **4** (R = Ph) in THF produced **3** (R = Ph) quantitatively, which was characterized by IR bands at 1696 and 1686 cm^{-1} ($CHCl_3$)[4]. Dropwise addition of the equimolar amount of a pre-cooled Grignard reagent in THF to this solution at −78 to −100 °C results in the *C*-addition product **2** in 50—85% yield (Table 1). **4** can also be transformed directly into **2** using two equivalents of R'MgX.

Use of the *N*-benzoyl group and working at low temperatures hinder side reactions such as addition of the organometallic components at nitrogen, attack at the ester groups, as well as radical reduction to **1**, and dimerization to **5**.

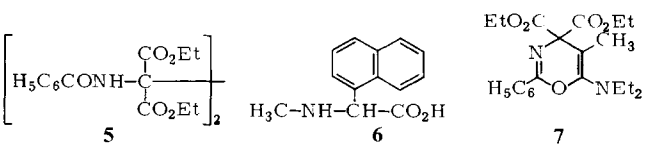


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Table 1. Yields and melting points of selected products **2** formed in the reaction of **3** or **4** with *C*-nucleophiles [a].

	R [b]	R′	*C*-Nucleophile	Yield [%]	M.p. [°C]
2a	Ph	Me	MeLi	78	47
			MeMgBr	70	
2b	Ph	*n*-Bu	*n*-BuLi	66	54
2d	Ph	1-naphthyl	1-naphthyl-MgBr	70–77	145–146
2e	Ph	2-pyridyl	2-pyridyl-Li	50	114–115
2f	Ph′	H_2C=CH—	H_2C=CHMgBr	54	86–87
2g	Ph	Ph—C≡C—	Ph—C≡CMgBr	61	51–52
2h	Ph	O_2NCH_2—	$MeNO_2$/EtN(*i*Pr)$_2$	88	77
2j	Me	2-oxo-1-cyclopentyl	1-morpholino-cyclopentene	72	120.5
2m	Ph	MeO_2C—CH(CN)—	MeO_2CCH_2CN/Base	92	oil
2o	Ph	Ph_3P=C(CO_2Et)—	Ph_3P=$CHCO_2Et$	97.5	120–123
2p	Ph	Et_2NCO—CH(Me)—	Me—C≡C—NEt_2	68	Resin

[a] All compounds gave satisfactory elemental analyses and spectroscopic data. [b] Ph′ = *p*-chlorophenyl.

The new method also permits the ready synthesis of *N*-alkyl-α-amino acids. For this purpose the crude product obtained after addition of the Grignard compound to the benzoyliminomalonic ester **3** (R = Ph) is methylated with excess dimethyl sulfate in the presence of a little NaH (60 h, 30 °C). After hydrolysis and decarboxylation with 48% HBr, *N*-methyl-2-(1-naphthyl)glycine **6**, for example, is obtained in good overall yield. CH acidic compounds such as nitroalkanes also add smoothly to **3** in the presence of bases. With enamines, adducts which yield 2-oxoalkyl derivatives (*e.g.* **2j**) upon acidic work-up are formed. Diethyl(1-propynyl)amine reacts with **3** (R = Ph) to give the isolable cycloadduct **7**, which is hydrolyzed by 1 N HCl to give the amide **2p**.

Using the new method aryl-, heteroaryl-, alkenyl-, and alkynyl moieties can be introduced into benzoylaminomalonic esters, whereby the range of application of the classic Sörensen synthesis, which is limited to electrophiles, is considerably extended.

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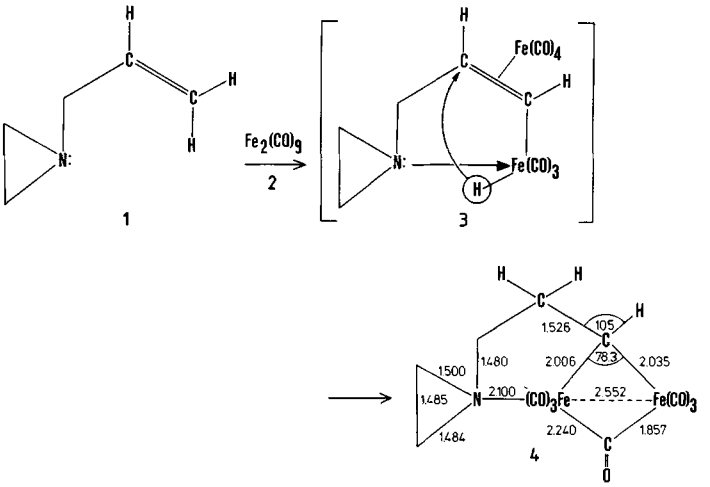
[4] Cf. F. Weygand, W. Steglich, I. Lengyel, F. Fraunberger, A. Meierhofer, W. Oettmeier, *Chem. Ber. 99* (1966) 1944; alkoxycarbonyliminomalonic esters: D. vor der Brück, R. Bühler, H. Plieninger, *Tetrahedron 28* (1972) 791; D. Seyferth, H. Shih, *J. Org. Chem. 39* (1974) 2336.

Doubly Metalated Carbon by Metal-Induced Vinyl-Ethylidene Rearrangement**

By *Rudolf Aumann**, *Gerald Henkel*, and *Bernt Krebs*

Metal complexes with multiply metalated carbon are of interest because of their structural relationship to intermediates reported to occur in methylene rearrangement reactions, the Fischer-Tropsch synthesis, and olefin metathesis[1]. We have previously reported on a twofold metalation by cleavage of two geminal C—C bonds[2] and now wish to describe a twofold metalation by metal-induced 1,2-migration of an olefinic C—H bond. Due to the "template effect", this reaction takes place at the γ-position to a donor atom: Thus, reaction of *N*-allylaziridine **1** with $Fe_2(CO)_9$ **2** in ether leads to formation of the μ-methylene complex **4** (red crystals, m.p. 86.5–87.5 °C; MS: $m/z = 391$; IR (hexane): ν(C≡O) 2067, 2016, 2000, 1989, 1965, 1932 cm^{-1}; ^{1}H-NMR ($C_6D_6/CS_2 = 1:2$): *H*CFe_2, $\delta = 8.05$ ($^3J = 4.5$, $^5J = 2.0$ Hz); ^{13}C-NMR ($CDCl_3$): *C*Fe_2, $\delta = 136.7$) as sole compound soluble in benzene in *ca.* 10–15% yield (Scheme 1).



Scheme 1. The bond lengths [Å] and bond angles [°] for **4** are given.

As precursor for **4** we postulate a dinuclear vinyl complex **3**, which isomerizes *via* π,σ rearrangement and migration of hydrogen from iron to the β-C atom to **4**. The methylene C-atom of **4** is bound symmetrically with almost equal bond lengths to the two Fe centers, which in turn are coupled by a strong bond (Fig. 1). The aziridine-N extends the coordination of Fe2, by the methylene-C, by three terminal CO- and one asymmetrically bound bridge CO-ligand, to a distorted octahedron. Fe1 is coordinated by the CH- and CO-bridges and by three terminal CO-ligands; there is also a weak bond to C7 (Fe—C 2.559(6) Å). The bonds in the aziridine ring of **4** are about the same length

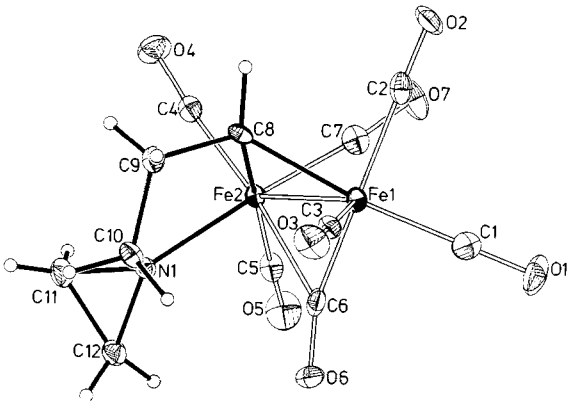


Fig. 1. Molecular structure of **4** in the crystal with vibration ellipsoids (30% probability). **4** crystallizes in the monoclinic system; space group $P2_1/c$ with $a = 13.307(2)$, $b = 9.225(2)$, $c = 13.329(2)$ Å, $\beta = 115.98(3)°$, $Z = 4$ (at −130 °C, $R = 0.044$).

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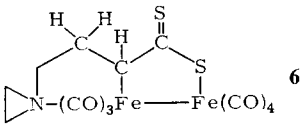
as those in the free aziridine (C—C 1.481(1), C—N 1.475(1) Å[4]), the C—N bond in the coordinated ring (mean value 1.491 Å) being somewhat longer.



6

4 slowly reacts with CS_2 in solution with *insertion* in a Fe—C bond to give **6** (identified by ^{1}H-NMR and MS measurements).

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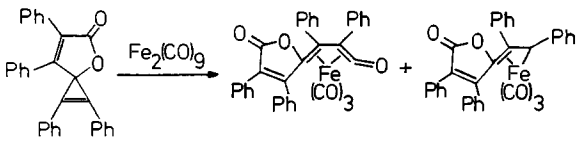
Cyclopropenes as Complex Ligands: $Fe_2(CO)_9$-Induced Ring-Opening of a Spirocyclopropene and Reversible CO-Addition to the Vinylcarbene Ligand

By *Jörg Klimes* and *Erwin Weiss**

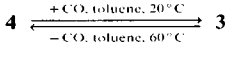
Cyclopropenes react with $Fe_2(CO)_9$ even at room temperature, with ring opening, CO-insertion, and formation of (η^3:η^1-allylcarbonyl)- or (η^4-vinylketene)$Fe(CO)_3$ complexes[1,2].

The spirocyclic lactone **2** reacts with $Fe_2(CO)_9$ in toluene (20 °C, 16 h)—as expected—to give the η^4-vinylketene complex **3** (10%); in addition, a novel η^3-vinylcarbene complex **4** (30%) was formed, the structure of which was determined by X-ray analysis (Fig. 1).



2 **3** **4**

The complex **4** is one of the few carbene(carbonyl)iron compounds not having a stabilizing heteroatom (O, N, S) on the carbene carbon atom. It is astonishingly stable towards atmospheric oxygen, does not decompose in boiling benzene, and rapidly adds CO (toluene, room temperature, normal pressure) to form **3**, a reaction which at 60 °C is reversible.



The carbonylation of a manganese-coordinated carbene to give the corresponding ketene complex has already been observed previously[7]—albeit at high pressures—and has been proposed as a model system for a partial step of the Fischer-Tropsch synthesis (carbene complex → ketene complex → aldehyde/alkohol)[9].

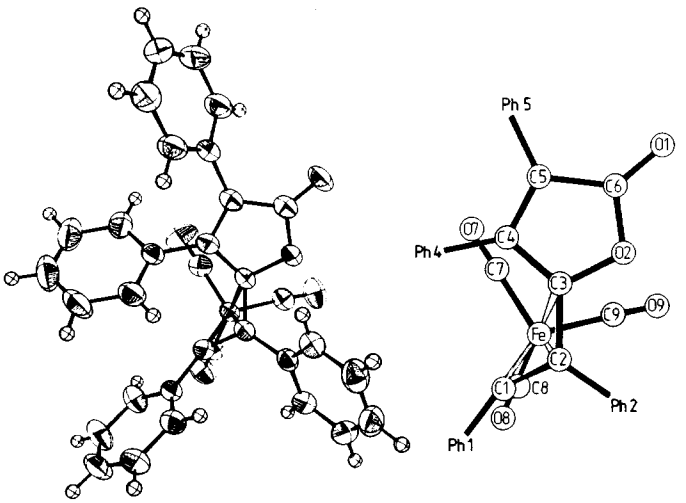


Fig. 1. Molecular structure of **4** in the crystal.

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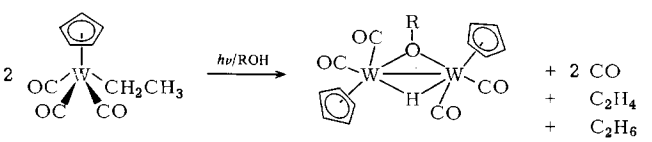
Photo-Induced Reaction of Alcohols with Tricarbonyl(η^5-cyclopentadienyl)ethyltungsten**

By *Helmut Guido Alt** and *Manfred Erwin Eichner*

The conversion of alcohols into μ-alkoxo-μ-hydrido transition metal complexes by activation of the OH bond at metal centers has previously succeeded only by thermal reaction of alcohols with multinuclear coordination compounds in solution[1].

In the photo-induced ($\lambda > 300$ nm, 2 h) reaction of the ethyl compound $C_5H_5W(CO)_3Et$ **1** with alcohols—*e.g.* methanol, ethanol and isopropyl alcohol—in pentane solution we have been able to isolate dinuclear species of the composition (μ-OR)(μ-H)$[C_5H_5W(CO)_2]_2$ **2** (**a**—**c**: R = Me, Et, *i*Pr) as main products (70—85%). The structure proposed for this type of compound is supported by elemental analysis and by mass, IR, ^{1}H-NMR and ^{13}C-NMR spectra.



1 **2**

The methoxo derivative **2a** shows the molecular ion ($m/z = 642$, referred to ^{184}W) in the mass spectrum. The four carbonyl bands in the IR spectrum (1932, 1903, 1830

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and 1810 cm^{-1} in Nujol) can be assigned to two terminal and two "semi-bridging" CO ligands, similarly as in the case of complexes of the type (μ-alkyne)$[C_5H_5Mo(CO)_2]_2$[2]. A single cyclopentadienyl resonance signal ($\delta_{C,H_5}=5.86$) also appears in the ^{1}H-NMR spectrum at low temperatures (−80 °C, [D$_6$]acetone), indicating a symmetric arrangement of the methoxo- ($\delta_{OCH_3}=4.32$) and the hydrido-bridge ligands [$\delta_{WHW}=-10.56$; $J_{W,H}=57.4$ Hz]. This is supported by the ^{13}C-NMR spectrum of **2a** at −80 °C ($\delta_{C,H_5}=93.7$, $\delta_{OCH_3}=83.6$, $\delta_{CO}=248.1/246.0$). In addition, the proton-coupled ^{13}C-NMR spectrum shows a spin-spin interaction of the μ-H ligand with only one 'sort' of CO ligand [$\delta_{CO}=246.0$; $J_{C,H}=8$ Hz].

On reaction with bromine or iodine (X_2) the dinuclear complexes **2** are quantitatively converted into the known[3] $C_5H_5W(CO)_2X_3$ derivatives.

^{1}H-NMR spectroscopic investigations show that both the hydrido complex $C_5H_5W(CO)_3H$ as well as the ethylene(hydrido) complex $C_5H_5W(CO)_2(C_2H_4)H$, which are formed by β-elimination during the photolysis of **1**[4], play an important role in the photo-induced reaction of **1** with alcohols. The compounds are obviously reactive, monomeric alcohol complexes of the type $C_5H_5W(CO)_2(ROH)H$, which eliminate ethane on reaction with **1** to give the dinuclear species **2**. As expected, the methyl derivative $C_5H_5W(CO)_3Me$ does not furnish **2a** in the analogous photoreaction with methanol.

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German version: *Angew. Chem. 94* (1982) 216

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"Dodecasils"—A Novel Series of Polytypic Clathrate Compounds of SiO_2

By *Hermann Gies, Friedrich Liebau**, and *Horst Gerke*

The known structural analogy between H_2O and SiO_2, which is illustrated by the fact that several ice modifications are isotypic with those of SiO_2, also covers inclusion compounds (clathrates) of both oxides. Thus, the rare mineral melanophlogite is analogous to the clathrate hydrates of the type I *i.e.* it is a "clathrasil" of formula $46SiO_2 \cdot 8M$ ($M=CH_4$, N_2, CO_2 *etc.*)[1]. We report here the synthesis, crystal structure, and thermal properties of "dodecasil-3C", a clathrasil which is isotypic[3] with the clathrate hydrates of type II[2].

$Si(OCH_3)_4$ is hydrolyzed in aqueous solution with $[N(CH_3)_4]OH$, and the homogeneous solution fused in SiO_2 ampules with Ar, Kr, Xe, CH_4, N_2, CO_2, N_2O, $N(CH_3)_3$, $HN(CH_3)_2$, or mixtures of these components and heated to 200 °C for several days.

The general structural formula of the product dodecasil-3C is $136SiO_2 \cdot 16X \cdot 8Y$; $[SiO_4]$ tetrahedra are edge-linked to form pentagondodecahedra (Fig. 1), which are in turn linked *via* common faces to form layers of approximate sixfold symmetry (Fig. 2). Neighboring layers are mutually displaced by $(\vec{a}_0+\vec{b}_0+\vec{c}_0)/3$ and are connected to form a cubic 3-layer structure[4].

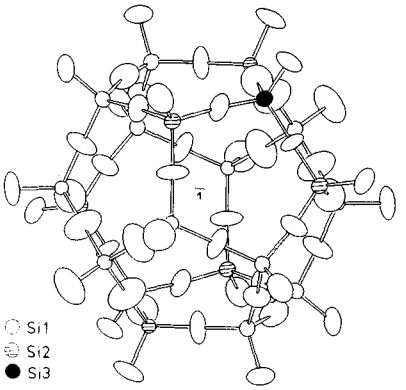

Fig. 1. Pentagondodecahedra in dodecasil-3C [X = CH_4, N_2; Y = $N(CH_3)_3$, $HN(CH_3)_2$]. Structure determination of a single crystal grown under (CH_4+N_2) using direct methods (SHELX-system): T_h^4-Fd3, $a_0=19.402(1)$ Å; 637 independent reflections, $R_w=0.064$, refined with anisotropic Si and O parameters; cages filled with guests, hydrogen atoms not considered.

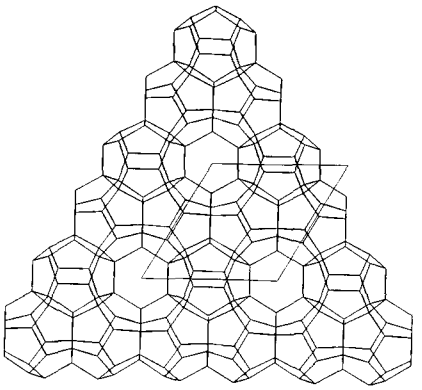

Fig. 2. Section of a layer of linked pentagondodecahedra of dodecasil-3C, parallel (111). The unit cell of the layer is indicated.

Every 16 pentagonododecahedra are linked to form a "super-tetrahedron". The nine upper pentagondodecahedra of Figure 2 represent a face of a super-tetrahedron of this type. This arrangement results in the formation of 8 further cavities, bounded by 16 faces (hexadecahedron). The incorporation of guest molecules into the SiO_2 framework was detected using room temperature mass spectroscopy. Electron density difference maps ($\rho_{obs}-\rho_{cal(Si,O)}$) of a dodecasil-3C crystallized under a (CH_4+N_2) atmosphere indicated that the small molecules CH_4 and N_2 could be assigned to the pentagondecahedral cages, and $N(CH_3)_3$ and $HN(CH_3)_2$ to the hexadecahedral cages. TGA studies of dodecasil-3C [X = Kr; Y = $N(CH_3)_3$, $HN(CH_3)_2$] and dodecasil-3C [X = N_2; Y = $N(CH_3)_3$, $HN(CH_3)_2$] at 950 °C indicated that these clathrasils are stable up to at least 950 °C, and after 3 h at this temperature do not release considerable amounts of guest molecules. N_2, Kr, $N(CH_3)_3$, and $HN(CH_3)_2$ were still detected in the mass spectrum after this type of thermal treatment. Analogous studies[5] on zeolite 5A indicated that incorporated guest molecules, such as Kr, were completely expelled after 30 min at 910 °C.

Apart from the cubic 3-layer structure of dodecasil-3C described here, the existence of further dodecasils with

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other layer sequences is to be expected. By analogy to the nomenclature of polytypes, the following symbols have been selected for dodecasil polytypes:

Symbol	Layer sequence	Symmetry	Lattice constants [Å] a_0	c_0
Dodecasil-1H	*A* A	hexagonal	13.8	11.2
Dodecasil-2H	*A B* A B	hexagonal	13.8	22.4
Dodecasil-3H	*A A B* A A B	hexagonal	13.8	33.6
Dodecasil-3C	*A B C* A B C	cubic	19.4	—
.	.	.	.	.
.	.	.	.	.
.	.	.	.	.
Dodecasil-D	disordered	"hexagonal"	13.8	non-periodic

Of these, we have obtained dodecasil-1H as single crystals. Clathrasils appear to be suitable as thermally stable, water- and acid-proof storage materials for radioactive noble gases produced in the generation of nuclear energy.

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Novel BN Ligand with Six Competing π Electrons around the Transition Metal Coordination Center**

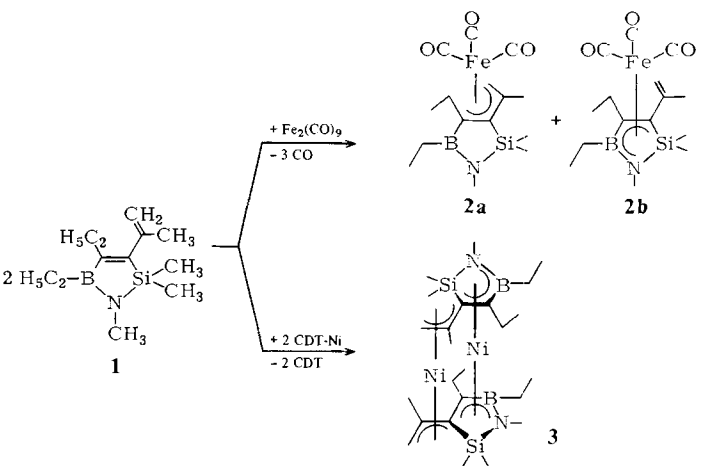
By *Roland Köster** and *Günter Seidel*

Hexaalkyl-Δ^3-1,2,5-azasilaborolines[1b] coordinate as 4π-ligands to transition metals[1a]. We have now synthesized in an analogous way[1b] the 3-vinyl-derivative **1** in order to investigate the complexation of the π bonds of the triene N=B—C=C—C=C which it contains.

Reaction of **1** ($\delta(^{11}B) = 46$)[2a] and nonacarbonyldiiron at 160 °C leads *via* cleavage of CO to formation of the mononuclear complexes **2a** (yellow, $\delta(^{11}B) = 50.3$[2a]) and **2b** (orange color, $\delta(^{11}B) = 18.2$[2a]) in 65% overall yield in the stable molar ratio 4 : 1. Composition and structure of these η^4-isomers are confirmed mass spectrometrically[2a] and by ^{1}H-NMR[2c] as well as ^{13}C-NMR spectroscopy[2a]. **2a** and **2b** can be separated from each other chromatographically (HPLC[2d]).

Reaction of *ttt*-1,5,9-cyclododecatrienenickel and **1** at *ca.* 80 °C affords the diamagnetic, red-black dinuclear sandwich complex **3** [m.p. 134—136 °C (dec.); mass spectrum[2b]: *m/z* 558 (Ni_2)], which is air-stable for a short time at room temperature. The ^{11}B-NMR signal of **3** [$\delta(^{11}B) = 26.4$[2a]] and the large shifts $\Delta\delta(^1H)$ and $\Delta\delta(^{13}C)$ of the two β-methylallyl groups of **3** compared to **1** clearly demonstrate that **3** contains two η^6-coordinated ligands. In the sandwich complex **3**, identified as isomerically pure on the basis of the MS[2b] and NMR data[2a,c], the two ligands **1** are held together by two central π-bonded nickel atoms.

As shown by the X-ray structure analysis[2e] of **3** [NiNi-distance 264.3(1) pm] the two ligands **1** are η^3/η^4-fixed to the Ni_2 dumbbell in a *syn*-arrangement to each other. The C^3 atoms of **1** each form a 2e/3c bond with both Ni atoms in **3**. The sequence of the ring atoms—reading clockwise—is different in each ligand **1**.



Apart from the transition metal π complexes with isolated bis(π-allyl)-structures[3] only a few compounds with linear[4] or crossed[5a] conjugated η^6-C_6 ligands are known. The bonding situation in **3** resembles that in bis(pentadienyl)dinickel[5b] with a cumulated electron system.

The competition of the π electrons of hetero- and homo-1,3,5-hexatrienes during complexation with transition metals—derivable from the structures of **2a**, **2b**, and **3**—opens up, *inter alia*, new prospects for catalysis and its control.

Procedure

2a and **2b**: A suspension of $Fe_2(CO)_9$ (2.07 g, 5.69 mmol) and **1** (2.89 g, 13 mmol) in mesitylene (10 mL) is heated under reflux (*ca.* 160 °C) for 3 h. 484 mL (21.6 mmol) of CO are liberated with concomitant formation of an Fe-mirror. After filtration (small amount of Fe) the solution is evaporated to dryness at ≤30 °C (bath)/10^{-3} torr and the residue sublimed at ≤60 °C/10^{-3} torr: 2.6 g (63%) of an orange-red, wax-like mixture (HPLC[2d]) of 78% **2a** and 22% **2b**, respectively.

3: The dark-red suspension of *ttt*-1,5,9-cyclododecatrienenickel (1.7 g, 7.7 mmol) and **1** (5.6 g, 25 mmol) is heated for 4 h at *ca.* 80 °C. After evaporation of the dark-brown suspension to dryness at ≤60 °C (bath)/10^{-3} torr the residue is crystallized from *ca.* 30 mL of pentane at −78 °C: 1.6 g (75%) of **3**, m.p. 134—135 °C (dec.).

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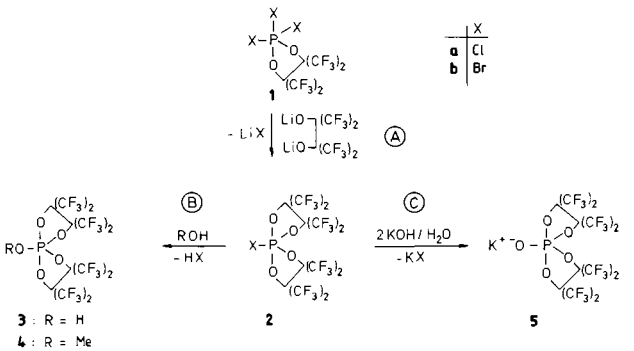
A Stable Tetraalkoxy(hydroxy)phosphorane and Phosphorane Oxide Anion by Hydrolysis of Tetraalkoxy(halogen)phosphoranes**

By *Gerd-Volker Röschenthaler** and *Werner Storzer*

Tetraalkoxy(hydroxy)phosphoranes were postulated as intermediates in the hydrolysis of alkyl(aryl)phosphates some time ago[1], but until now could only be synthesized in a few cases by oxidation of the corresponding hydrogen phosphoranes[2]. Hydrolysis of the halospirophosphoranes **2a** and **2b**, obtainable by treating the trihalophosphoranes[3a] **1a** and **1b** with dilithium perfluoropinacolate in neutral or alkaline aqueous ether solution, led to the hydroxyphosphorane **3** (m.p. = 72 °C, 78% yield) and potassium phosphorane oxide **5** (m.p. = 118 °C, 100% yield), respectively, without cleavage of the P—O ring bonds to form a P=O bond. A tautomeric monocyclic form[2] of **3** is not observed. The methoxy derivative **4** (m.p. = 68 °C, 92% yield) is obtained in the same way using methanol.



Scheme 1. Ⓐ 1 : 1; −196 to +160 °C (10 h) and +20 °C (24 h), respectively, petroleum ether extraction, Et_2O, sublimation: **2a** (62%, m.p. = 62 °C) and **2b** (43%, m.p. = 82 °C), respectively. Ⓑ 1 mL of water or methanol is added to a stirred solution of 0.003 mol **2a** or **2b** in 20 mL of Et_2O; after 30 min the organic phase is separated off and the aqueous phase extracted three times with ether. The mixture was then dried over Na_2SO_4, concentrated and the product recrystallized from Et_2O. Ⓒ 1.0 g of KOH in 5 mL of water is added to a stirred solution of 0.01 mol **2a** or **2b** in 30 mL of Et_2O; after 1 h the mixture is extracted three times with 20 mL of ether, dried over Na_2SO_4 and the solvent removed; yield 7.5 g **5**.

The ring-forming $OC(CF_3)_2C(CF_3)_2O$-substituents (electron withdrawing properties and spacial requirements of the CF_3 groups) produce the remarkable stability of **3**, **4**, and **5**. Hence, **3** can be sublimed out of concentrated sulfuric acid. The pK_a value was determined as 2.0[4].

The composition and constitution of all the novel compounds have been confirmed by elemental analysis, 70 eV mass spectra (apart from **5**), as well as by NMR spectra[5]. The highest mass ions are $M^+ - F$ for **2**, **3**, and **4**, and the most frequent fragment is CF_3^+ for **2** and **3**, and $M^+ - CF_3$ for **4**. The $\delta(^{31}P)$ values are typical of phosphoranes [−12.4 (**2a**), −37.9 (**2b**), −34.5 (**3**), −34.5 (**4**), −37.9 (**5**)]. From the $\delta(^{19}F)$ values it is clear that different sets of CF_3 groups are present in **2a**, **2b**, and **5** [−65.1, −65.6 (**2a**); −67.5, −68.0 (**2b**); −68.7, −69.4 (**5**)] since the first step of a ligand permutation process is slow on the time scale of the NMR experiment[3b]. The $\delta(^1H)$ values for **3** and **4** are 10.8 and 4.00, respectively ($^3J_{PH} = 15.1$ Hz).

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Vehicle Mechanism, A New Model for the Interpretation of the Conductivity of Fast Proton Conductors

By *Klaus-Dieter Kreuer, Albrecht Rabenau**, and *Werner Weppner*

The conduction of protons in solids is generally explained, as in the case of liquid electrolytes, in terms of the Grotthuss Mechanism[1]: The protons move in an infinite network of hydrogen bonds. The process consists of two steps, the translation of a proton from an oxonium ion[2] to a water molecule by tunneling in a hydrogen bond and subsequent reorientation (rotation) of the water molecule thus formed in order to be able to take up the next proton (Fig. 1, top).

Our investigations lead to strong arguments in favor of another process, which we call the Vehicle Mechanism. According to this model the proton does not migrate as H^+ but as OH_3^+, NH_4^+, *etc.*, bonded to a "vehicle" such as H_2O, NH_3, *etc.* The "unladen" vehicles move in the opposite direction (Fig. 1, bottom). The vehicle shows a diffusion coefficient corresponding to the proton conduction and behaves like a Brønsted base (proton acceptor) towards its crystallographic environment.

Fig. 1. Model of proton conduction. Top: Grotthuss Mechanism; the protons are passed along the hydrogen bonds. Bottom: Vehicle Mechanism: the movement takes place with the aid of a moving "vehicle", *e.g.*, H_2O or NH_3 as complex ion (H_3O^+ or NH_4^+).

The Nernst-Einstein relation between the diffusion (translation) of the vehicle and the conductivity of protons is fulfilled, but no correlation between the rotation of the vehicle and the conductivity has been found (Table 1).

The Vehicle Mechanism makes the extremely large temperature factors which have been observed in X-ray and neutron diffraction studies understandable[1b] and is consistent with the observation that practically all good proton

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Table 1. Comparison of data derived from determinations of the ionic conductivity, rotational (Grotthuss Mechanism) and translational (Vehicle Mechanism) modes for two proton conductors.

Compound	Process	Activation Enthalpy [eV]	Jump Frequency at Room Temperature [s^{-1}]	Measurement
$HUO_2AsO_4 \cdot 4H_2O$	conductivity	0.64 ± 0.03	10^9	complex impedance
	H_2O rotation	0.27 ± 0.02	10^6	^{1}H-NMR [a]
	H_2O translation	0.8 ± 0.2	3×10^9	^{18}O self-diffusion, H_2O desorption
$LiN_2H_5SO_4$	conductivity	0.75 ± 0.07	—	complex impedance [4]
	$-NH_3^+$ rotation	0.19 ± 0.01	—	^{1}H-NMR [5]
	$N_2H_5^+$ translation	0.7 ± 0.04	—	^{1}H-NMR [5]

[a] In collaboration with *R. Messer*, Max-Planck-Institut für Metallforschung, Stuttgart.

conductors are good ion-exchangers, in which oxonium ions are always exchanged, but individual protons never, *e.g.*,

$$HUO_2AsO_4 \cdot 4H_2O + Na^+ \rightleftharpoons NaUO_2AsO_4 \cdot 3H_2O + H_3O^+$$

Using the Vehicle Mechanism as a working principle a series of new proton conductors have been found[3a]. In particular proton conduction in zeolites has been optimized. Since the Vehicle Mechanism no longer requires an infinite hydrogen bond network, much stronger basic species, *e.g.* NH_3, which have a high self-diffusion coefficient, can be used. In the case of zeolites this is particularly important, since NH_3, in contrast to H_2O, is capable of binding a proton from the amphoteric host lattice with formation of NH_4^+.

The concept of the Vehicle Mechanism leads to new applications of solid proton conductors in electrochemical cells[3b]. Whereas the previously discussed mechanisms are based on pure proton transport between electrodes of different H-activity—as, *e.g.*, mixed conducting hydrides—electrodes of different oxygen activity can now also be taken into consideration. The transport of protons and water molecules in opposite direction give together an overall transport of O^{2-}. For example, proton conductors have already been used as electrolytes in metal-air and metal/metal oxide cells (Table 2).

Table 2. Properties of some galvanic elements with hydrated NH_4-zeolite A as separator material.

Anode	Cathode	Observed Open Cell Potential [V]	Observed Short Circuit Current Density [$\mu A\ cm^{-2}$]
Fe	MnO_2	0.7—1.2	120
Sn	MnO_2	0.85	80
Zn	MnO_2	1.3	800
Zn	PbO_2	1.7	5000

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Photochemical Oxidative Addition of Chlorine from Chloroform to 2,2′-Bipyridyldichloroplatinum(II)**

By *Arnd Vogler** and *Horst Kunkely*

The mechanism of light-induced multielectron transfer has been little studied. Increasing interest is being shown in reactions of this type in relation to photosynthesis, or to the photochemical splitting of water. Particularly important two-electron redox reactions of complexes are reductive elimination and oxidative addition. Some light-induced reductive eliminations have been studied in depth[1a]. In addition, a series of photolytic oxidative additions is known[1b]. However, in all cases the primary photochemical step consists of the release of a ligand. Consequently, oxidative addition is not strictly a photochemical reaction, but occurs more frequently as a thermal reaction at coordinatively unsaturated, reactive metal complexes. We report the first oxidative addition as the primary step in a photochemical reaction.

Irradiation of $[Pt^{II}(bpy)Cl_2]$[2] in acetonitrile led, in the absence of side-reactions, to substitution of chloride with formation of $[Pt(bpy)(CH_3CN)Cl]^{\oplus}$; irradiation at the long wavelength band of the complex ($\lambda \geq 320$ nm) was sufficient. The reaction did not proceed in $CHCl_3$ solutions. In contrast $[Pt^{II}(bpy)Cl_2]$ is smoothly oxidized to

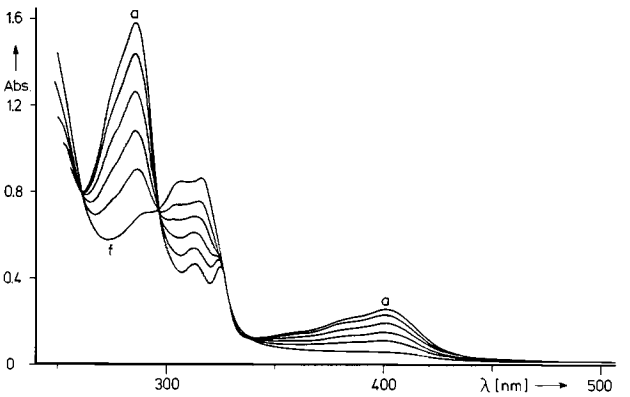

Fig. 1. Changes in the absorption spectrum during photolysis of $[Pt(bpy)Cl_2]$ (8.78×10^{-5} mol/L) in $CHCl_3$ in a 1 cm cuvette, excitation light: $\lambda > 280$ nm, irradiation time: a = 0, f = 10 min.

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$[Pt^{IV}(bpy)Cl_4]$[2] when shorter wavelength light ($280 < \lambda < 300$ nm) is used for the irradiation. The spectral changes during photolysis (Fig. 1) can be simulated by oxidation of $[Pt(bpy)Cl_2]$ with Cl_2, or by reduction of $[Pt(bpy)Cl_4]$ with $NaBH_4$. The quantum yield of the photooxidation was $\phi = 0.06$ for irradiation with $\lambda = 280$ nm.

From these results it is improbable that a coordinatively unsaturated complex is formed in the primary photochemical step by release of a ligand. Summarizing, the following mechanism is proposed:

$$[Pt^{II}(bpy)Cl_2] + CHCl_3 \xrightarrow{h\nu} [Pt^{III}(bpy)Cl_3] + {}^{\circ}CHCl_2$$

$$[Pt^{III}(bpy)Cl_3] + {}^{\circ}CHCl_2 \longrightarrow [Pt^{IV}(bpy)Cl_3]^{\oplus} + CHCl_2^{\ominus}$$

$$[Pt^{IV}(bpy)Cl_3]^{\ominus} + CHCl_2^{\ominus} \longrightarrow [Pt^{IV}(bpy)Cl_4] + :CHCl$$

Two-electron reductions are well known for geminal dichlorides CR_2Cl_2[3]. In the initial step an electron is taken up *via* formation of ${}^{\circ}CR_2Cl$ and $Cl^{\ominus}$. The radicals ${}^{\circ}CR_2Cl$ are powerful oxidizing agents, which are able to rapidly add a further electron to form the $CR_2Cl^{\ominus}$ anion. This reaction mechanism is thus to be expected in all cases involving the reaction of geminal dichlorides with a two-electron reducing agent such as Pt^{II}. Presumably the intermediate products $[Pt^{III}(bpy)Cl_3]$ and ${}^{\circ}CHCl_2$ have a very short lifetime and rapidly exchange a further electron to form Pt^{IV}. In accord with this assumption radicals could not be detected during the photolysis. ESR signals could neither be registered during low temperature photolysis at 77 K nor by irradiation at room temperature in the presence of *N*-benzylidene-*tert*-butylamine *N*-oxide (*N*-*tert*-butylphenylnitron) as spin trap.

In the last step of the oxidative addition, the anion $CHCl_2^{\ominus}$ could add directly as a sixth ligand to the coordinatively unsaturated complex $[Pt^{IV}(bpy)Cl_3]^{\ominus}$ to form $[Pt^{IV}(bpy)Cl_3(CHCl_2)]$. This type of oxidative addition of chlorinated alkanes such as dichloromethane to Pt^{II} complexes is a well known thermal reaction[4]. In our example, however, the complex removes a chloride ion from the anion $CHCl_2^{\ominus}$. Thereby $[Pt^{IV}(bpy)Cl_4]$ is formed as a stable end product together with monochlorocarbene. Apparently, this carbene reacts with a further chloroform molecule by insertion into its C—Cl bond resulting in formation of 1,1,2,2-tetrachloroethane, which was detected by gas chromatography. This insertion reaction is a well known reaction type of carbenes[5]. Attempts to trap the monochlorocarbene with 2,3-dimethyl-2-butene did not lead to unambiguous results. At low concentrations of olefin (*ca.* 10^{-3} mol/L) the carbene reacts preferentially with solvent. With markedly higher concentrations of olefin the solubility of the complex is too low. In addition, complications from substitution reactions arise.

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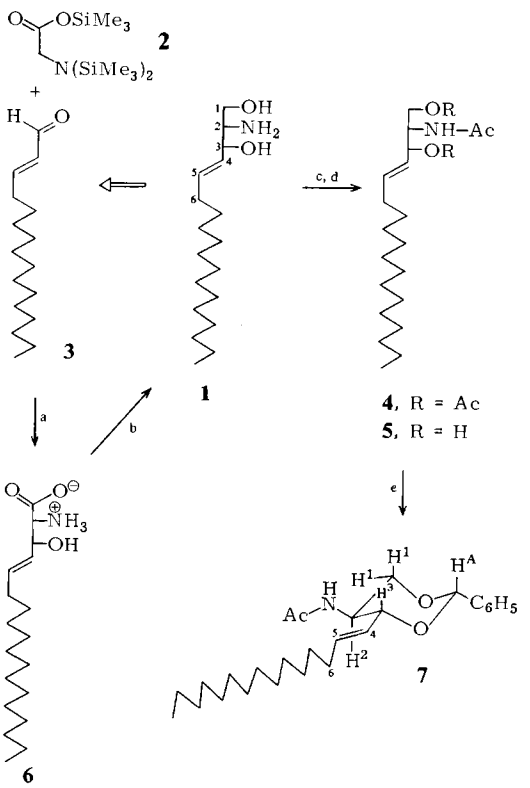
Diastereoselective Synthesis of D,L-Sphingosine**

By *Richard R. Schmidt** and *Rudolf Kläger*

Sphingosine **1**, an important membrane component, was previously accessible from achiral educts only *via* several steps involving formation of *threo*- and *erythro*-products[1, 2]. The natural product could be prepared—albeit in low yields—in more than ten steps from D-glucose[3]. According to the progress made in the diastereoselective synthesis of acyclic systems[4] it should be possible to prepare *erythro*-configurated D,L-sphingosine.



Scheme 1. a: LDA in THF, −80 °C, 1.5 h; yield 59—75% **6**, m.p. = 192—193 °C (dec.) from DMF.—b: 7 equiv. $LiAlH_4$ in THF, reflux, 36 h; yield 90% **1**; $R_F = 0.2$ (DC, silica gel, $CHCl_3$: methanol = 1 : 1).—c: pyridine/Ac_2O, RT, 15 h; yield 50% **4**; m.p. = 90—91 °C (Lit. [1]: 91—92 °C).—d: NaOMe in MeOH, RT, 1 h; yield 91% **5**; m.p. = 85—87 °C.—e: 3 equiv. C_6H_5—CHO and 1 equiv. $ZnCl_2$ in toluene, RT, 16 h; yield 89% **7**, m.p. = 114—115 °C from petroleum ether (40—60 °C)/ethyl acetate = 50 : 1.

We allowed the α,β-unsaturated C_{16}-aldehyde **3** to react with the α-carbanion of the protected glycine **2** (Scheme 1), since good results had already been achieved in this reaction with simple aldehydes[6]. The *erythro*-configurated, unsaturated β-hydroxy-α-amino acid **6** was formed exclusively.

The structure of **6** was confirmed by reduction with $LiAlH_4$ to the D,L-sphingosine **1** (90%) and conversion of the latter into the triacetyl derivative **4**[1]. Moreover, cleavage of the *O*-acetyl groups to give **5** and subsequent reaction with benzaldehyde afforded a 1,3-dioxane derivative **7**; the *trans* arrangement of H^2 and H^3, as is expected for the *erythro*-configuration, is demonstrated in the ^{1}H-NMR spectrum by the typical coupling constant of 8.9 Hz for

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such protons. Since a method for the resolution of D,L-sphingosine **1** is already available, the synthesis of natural sphingosine is possible in the above mentioned way in three steps.

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Selective C—H Bond Activation in Ethane Using Photoexcited Cu Atoms**

By *Geoffrey A. Ozin**, *Steven A. Mitchell*, and *Jamie García-Prieto*

In the general area of hydrocarbon conversions, reactions involving the selective cleavage of C—H and C—C bonds are of considerable industrial importance[1], but have been investigated only to a limited extent.

We report on the resonance excitation of the $^2P \leftarrow ^2S$ electronic transition of Cu atoms in the presence of ethane at 12 K, and on the subsequent reactions which promote the selective insertion of Cu atoms into the C—H bonds of ethane; in contrast, the C—C bond is not attacked.

Figure 1 (A and B) shows the UV-VIS spectra following deposition of a Cu/C_2H_6 mixture ($1:10^4$) at 12 K, and after annealing at 30 K. The splitting of the $^2P \leftarrow ^2S$ band of Cu atoms at *ca.* 320 nm in the 30 K spectrum (4315 cm^{-1}) is exceptionally large compared with the corresponding splittings for gaseous Cu atoms (284 cm^{-1}) and Cu atoms in rare gas (*e.g.* Ar, 760 cm^{-1}) and methane (2055 cm^{-1}) matrices. This is indicative of a rather strong interaction between the excited Cu atoms and the surrounding "ethane cage".

Irradiation (10 nm band-width at half height) of the Cu/C_2H_6 matrix at 12 K causes rapid first order decay of all Cu atom lines and simultaneous appearance of new bands at 330, 260, 230, and 220 nm (Fig. 1C). The overall picture bears a striking resemblance to the first order photokinetic decay and optical spectroscopic observations of excited Cu atoms in solid CH_4[6].

ESR studies indicated that irradiation at 320 nm causes rapid bleaching of all the Cu atom signals and concomitant growth of a strong multiplet signal around the free electron *g*-factor with the characteristic hyperfine pattern of C_2H_5 radicals[10]. Groups of much weaker lines to the low- and high-field side of the free electron *g*-factor appear in addition to the C_2H_5 radical; these disappear, however, in the course of the photolysis.

The evolution and spectral form of this intermediate species are reminiscent of the H_3CCuH primary photoinsertion product observed in the Cu/CH_4 system, implying that H_5C_2CuH probably occurs as an intermediate.

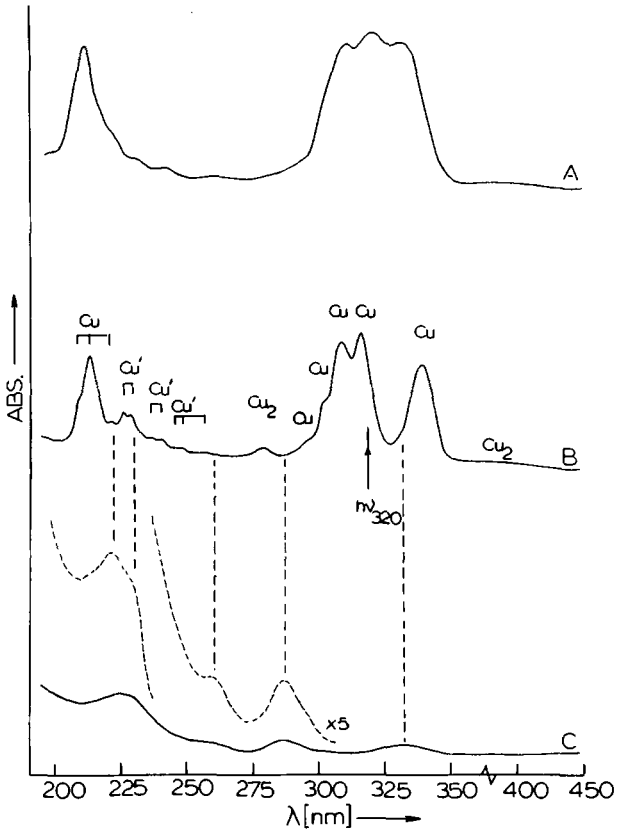

Fig. 1. UV-VIS spectra of Cu/C_2H_6 mixture ($1:10^4$) at 12 K (A), after annealing at 30 K (B), and (C) after photoexcitation (320 nm) at 12 K (*C*).

IR spectroscopic studies of UV-excited Cu/C_2H_6 matrices clearly identified CuH as a photoproduct (band at 1840 cm^{-1}). A weak stretching mode at 1690 cm^{-1} (νCuH) is tentatively ascribed to the proposed photoinsertion product H_5C_2CuH (H_3CCuH: $\nu CuH = 1697$ cm^{-1}[6]). In agreement with earlier studies, we found the IR absorbance of matrix isolated C_2H_5 radicals to be very weak[13]. All these results are, therefore, consistent with the following mechanism:

$$Cu(^2S)/C_2H_6 \xrightarrow[12\ K]{h\nu(300-340\,nm)} Cu(^2P)(C_2H_6) \xrightarrow{\text{photoinsertion}} H_5C_2CuH \xrightarrow{\text{secondary photolysis}} H_5C_2^{\odot} + CuH$$

Of particular significance in this study is that H_3CCuCH_3, H_3CCu, or $H_3C^{\odot}$ were not observed, which indicates that C—H bond insertion processes are highly favored over C—C bond insertion or cleavage reactions. The similar behavior of excited Cu atoms in CH_4 and C_2H_6 matrices supports the assumption that insertion into the C—H bond is the primary photochemical step.

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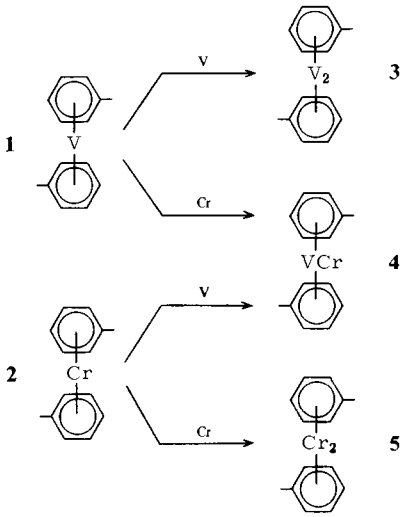
Arene-Metal Clusters: Metal Atom-Bis(arene)metal Solution Phase Chemistry**

By *Geoffrey A. Ozin** and *Mark P. Andrews*

Liquid organomono-[1], di-[2] and trimetallic polymers[3] have recently been synthesized at 250 K from transition metal atoms and poly(methylphenylsiloxane) (DC 510). Subsequent experiments led to the discovery of liquid polymer-stabilized parent members of series of homologous homo- and heterometallic clusters[2,4].

We have now investigated the initial stages of cluster formation in DC 510 and similar systems, whereby aggregates of composition $(arene)_nM_m$ are formed. The procedure employed in this study involved the reaction of pure samples of bis(toluene)vanadium **1** or bis(toluene)chromium **2** in methylcyclohexane solution at 140—160 K with vanadium or chromium atoms (metal atom microsolution method)[12]. Since the dimetal compounds **3—5** absorb at considerably longer wavelengths than the metal ligand charge transfer (MLCT) bands of complexes **1** and **2**, reactions can be followed by UV spectroscopy.

The absorption spectra of purified samples of **1** and **2** (synthesized both by Fisher-Hafner and metal atom methods) show very intense MLCT transitions at 324 and 318 nm, respectively. A solution of **1** in methylcyclohexane at 140 K reacts with V atoms to give the divanadium compound **3**, which absorbs at 453 nm (Scheme 1)[2-4]; **1** reacts with Cr atoms to give the heterodimetallic species **4**, which absorbs at 420 nm. The latter wavelength is the same as that attributed to CrV produced by co-condensation of atomic Cr and V into DC 510 (250 K)[2-4].

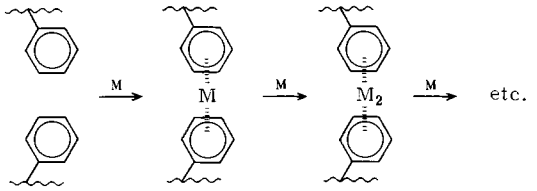


Scheme 1.

Similarly, Cr and V atoms react with the complex **2**; **2** reacts with Cr to give **5**, which absorbs at 405 nm, paralleling the observations made for the Cr/DC 510 system[2,4].

Since we found no evidence for free arene or metal displacement reactions, the dimetallic species **3—5** were probably formed by direct addition of a metal atom to the metal center of $(toluene)_2M$.

Based on our new results we propose that arene-stabilized dimetal complexes are produced *via* one-step addition of a metal atom to a bis(arene)metal target center, and that formation of dimetallic, trimetallic and higher clusters in DC 510 is a process proceeding from a parent bis(arene)transition-metal complex to higher nuclearity metal clusters as shown in Scheme 2.



Scheme 2.

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The Cycloaddition of Carbonyl-Flanked Methylene Bridges— A Novel Method for the Synthesis of Metallacycles**

By *Christine Bauer, Ernst Guggolz, Wolfgang A. Herrmann*, Gangolf Kriechbaum*, and *Manfred L. Ziegler*

Carbene additions to metal-metal multiple bonds using diazoalkanes as starting compounds usually lead without difficulty to dimetallacyclopropanes. We now report on an exceptional case—the first cycloaddition of ketocarbenes to a coordinatively unsaturated carbonylmetal compound.

According to earlier findings[1,5,7,10b] it was expected that α-diazoketones **2a-d** would react with the dirhodium compound **1** to form the dimetallacyclopropanes **3a-d.** Indeed, **1** reacts rapidly with **2a-d** at −40 to +25 °C with quantitative elimination of N_2, but, instead of **3a-d,** their novel constitutional isomers **4a-d** are formed exclusively (isolated yields 80—95%). A single crystal X-ray structural analysis was carried out on **4a** (Fig. 2).

Figure 2 shows that the ketocarbene derived from **2a,** beyond conventional μ,η¹-fixation to the Rh=Rh bond of

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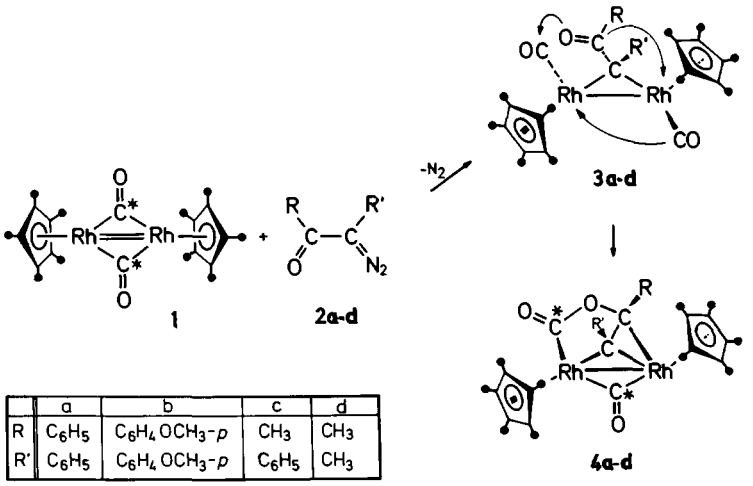
[**] Part 25 of the series, Transition Metal-Methylene Complexes. This work was supported by the Fonds der Chemischen Industrie, The Deutsche Forschungsgemeinschaft, and the Chemische Werke Hüls.—Part 24: [1].



	a	b	c	d
R	C_6H_5	$C_6H_4OCH_3$-*p*	CH_3	CH_3
R'	C_6H_5	$C_6H_4OCH_3$-*p*	C_6H_5	CH_3

1, adds *via* the oxygen atom to a carbon monoxide ligand. This bond [C(1)—O(2)] completes a five-membered, nonplanar metallacycle. In addition, the keto C-atom C(3) is coordinated to Rh(2), while the remaining CO group unsymmetrically bridges the RhRh single bond. Despite the practically equal Rh(1)—C(4) and Rh(2)—C(4) bond lengths (202.8(7) and 205.6(6) pm, respectively), as present in typical μ-methylenedirhodium complexes[5, 7, 10b], the angle θ (61.7°) between the Rh(1)—Rh(2) vector and the plane defined by C(3), C(4), C(41) does not fulfil the orthogonality criterion of this class of compounds. The methylene character of the ketocarbene derived from **2a** is thus essentially lost in favor of formation of a π-olefin-like coordination of C(3) and C(4) to Rh(2). It is confirmed by ^{13}CO labeling that the keto functions of **2a—d** preserve their identity during the synthesis of **4a—d.**

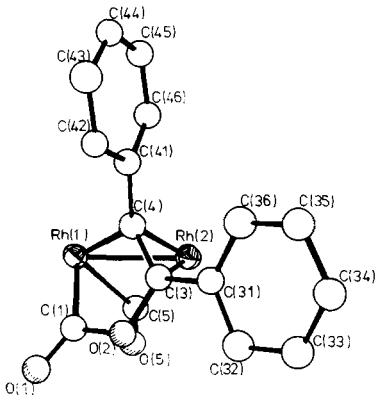


Fig. 2. ORTEP diagram of the structure of **4a** (without the centrally bound C_5Me_5 ligands) in the crystal.—**4a:** IR (ν(CO); cm^{-1}): 1813 vs, 1695 vs [THF]; 1815 vs, 1690 vs [KBr]. [^{13}CO]-**4a** has additional bands at 1773, 1655 [THF] and 1770, 1645 [KBr].—^1H-NMR (90 MHz, 25°C, [D_8]THF, int. TMS): δ(CH_3) 1.52 (s, 30H), δ(C_6H_5) 6.80—7.25 (m, 10H).—$^{13}C\{^1H\}$-NMR (22.63 MHz, 30°C, CD_2Cl_2, *ca.* 45% ^{13}CO-enrichment): δ(CH_3) 9.16, 8.51 (s); δ($C_5(CH_3)_5$) 103.73, 109.83 (d; $^1J_{Rh,C}$ = 4.9 Hz); δ(C_6H_5) 125.09, 126.41, 126.70, 127.85, 129.07, 137.5, 146.68; δ(C(4)) ≈ 169 (m); δ(C(1)) 190.82 (dt; $^1J_{Rh,C}$ = 52 Hz); δ(C(5)) 227.17 (ABXY-system with A = C(1), B = C(5), X, Y = Rh(1) and Rh(2); $^1J_{Rh,C}$ = 58 Hz).—FD-MS (from acetone): *m/z* 726 (molecular ion).—In the ^1H-NMR spectrum (CD_2Cl_2) of **4b** the $C_5(CH_3)_5$- and $C_6H_4OCH_3$-protons are also nonequivalent (δ 1.52, 1.53 and 3.69, 3.87, singlets).

In order to synthesize the metallacycles **4a—d** *via* the μ-methylene derivatives **3a—d** the following obstacles must be overcome: 1) The ketocarbene group of **2** or **3** may not be part of a rigid ring system that prevents twisting of the two ligand halves about the C(3)—C(4) bond. As a key example, compound **3** having a 1,3-dioxoindan-2-ylidene bridge that resists intramolecular cyclization even under drastic conditions may be cited[9].—2) The cyclization **3**→**4** calls for keto groups with strongly nucleophilic oxygen atoms, as has been demonstrated by internal competition experiments. Thus, if **1** is treated with **2e,** then *exclusively*

$C_2H_5OCO—C(=N_2)—C(=O)—COOC_2H_5$ **2e**

the keto O-atom, but not an ester O-atom adds to the CO ligand during the formation of **4e** (X-ray structure analysis). Consistent with this finding, subsequent intramolecular cycloaddition of the stable complexes [μ-$C(CO_2Alkyl)_2$][(η^5-C_5Me_5)Rh(CO)]$_2$ fails[5, 7, 10b]. According to IR spectroscopic investigations, reaction of **1** with **2e** rapidly forms **3e** at −78°C, which compound is subsequently converted at *ca.* −30°C into **4e.**—3) The ring-closure reactions analogously call for sufficiently electrophilic CO ligands. This explains why the cobalt analog of **1** does not yield cycloadducts of type **4** on reaction with **2a—e.**

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A New Route to Pyridine Derivatives: Reaction of *N*-Methylene-*tert*-butylamine with Enamines**

By *Mitsuo Komatsu**, *Hideo Ohgishi, Shigeki Takamatsu, Yoshiki Ohshiro,* and *Toshio Agawa*

We report a new and mechanistically novel synthetic method for 3,5-disubstituted pyridines[2]. The present process is characterized by high conversions and ready availability of starting materials.

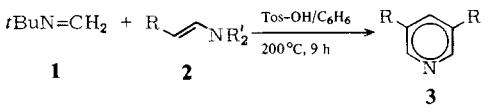

Table 1. Preparation of 3,5-disubstituted pyridines **3.**

	R	NR'_2	Catalyst	Yield [%] [a]
a	Me	piperidino	tos-OH	67
b	Et	piperidino	tos-OH	72
c	*i*-Pr	piperidino	tos-OH	78
d	*c*-C_6H_{11}	piperidino	—	85
e	Ph	morpholino	—	73
f	PhS	dimethylamino	tos-OH	87

[a] Yields determined by ^1H-NMR spectroscopy; yields of isolated products were 0-20% lower than these values.

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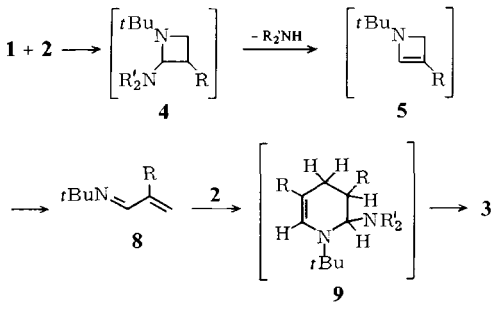
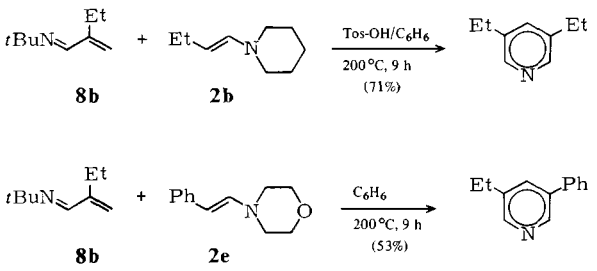
The pyridine derivatives **3** are easily obtained by heating *N*-methylene-*tert*-butylamine **1**[3] and enamines **2** (1:2 molar ratio) in the presence of *p*-toluenesulfonic acid (0.03 equiv.) (Table 1). The method can also be used for enamines having bulky substituents (Ph, *c*-C_6H_{11}).



We presume that the reaction proceeds *via* the intermediate azadiene **8**, which undergoes cycloaddition[4] with enamine **2** to give the tetrahydropyridine **9**. Subsequent thermal- or acid-catalyzed cleavage of R'_2NH, $CH_2{=}C(CH_3)_2$, and H_2 from **9** leads to the aromatic pyridine derivatives.



The intermediate **8** could be isolated in 13—53% yield under milder conditions when the substituent R is less bulky. Reaction of **8b** with 1-butenylpiperidine to give 3,5-diethylpyridine confirms the suggested mechanism. The reaction also offers a preparative route to unsymmetrical 3,5-disubstituted pyridines, as indicated by the reaction of **8b** with 1-styrylmorpholine to give 3-ethyl-5-phenylpyridine.

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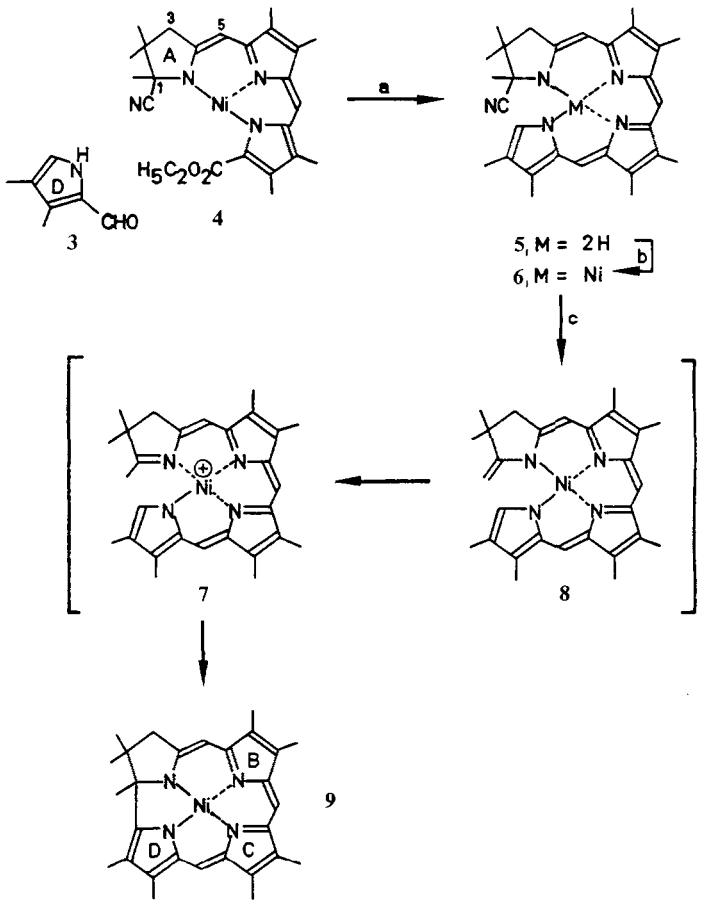
(A→D) Ring Closure to the Nickel(II)-B,C,D-Hexadehydrocorrinate**

By *Franz-Peter Montforts**

Direct coupling of rings A and D is an essential structural element of the corrins. The multiplicity of their modes of formation by cyclization is important regarding the question of the origin of the corrin structure[1]. The spectrum of ring closure reactions extends from the photochemical A→D cycloisomerization, a key step in the synthesis of vitamin B_{12}, to the acid-catalyzed dehydrobilin cyclizations, which yield the corroles and octadehydrocorrins. The B,C,D-hexadehydrocorrin-type **9**[6] has so far been a missing member of the corrin family. We report here on the synthesis of a correspondingly protected secocorrin **6** and its convenient cyclization to **9** (Scheme 1).



Scheme 1. Reaction conditions: a: 1) **4** in tetrahydrofuran (THF + 100 eq. KOH in CH_3OH-H_2O (9:1), reflux, under argon (hydrolysis of the ethyl ester), crude work-up; 2) +2.5 eq. **3** + 9 eq. *p*-toluenesulfonic acid in $CHCl_3$, reflux, under argon (50% crystalline), b: 4 eq. $Ni(CH_3CO_2)_2 \cdot 4H_2O$ + 28.5 eq. sodium acetate in CH_3OH-THF (2:1), room temperature (69% crystalline). c: 1) 100 eq. KO*t*Bu in *t*BuOH (degassed) 70°C, under argon; 2) KH_2PO_4, H_2O, CH_2Cl_2, extraction (73% crystalline). Selected UV/VIS data of **6** and **9**: **6** ($CHCl_3$): λ_{max} = 405 nm ($\log\varepsilon$ = 4.60), 726 (4.35). — **9** ($CHCl_3$): 405 (4.56), 765 (4.21).

Alkaline hydrolysis of the ester function of the nickel complex **4**[7], followed by acid-catalyzed condensation with decarboxylation and decomplexation with the pyrrolecarbaldehyde **3**[8] furnishes the tetracyclic ligand **5**, which is recomplexed with nickel acetate to give **6**. Base-induced elimination of the cyanide group to give **8** and, most likely, subsequent protonation[2d,9] of the 1-methylene group leads to **7**, which cyclizes, and after deprotonation yields **9**.

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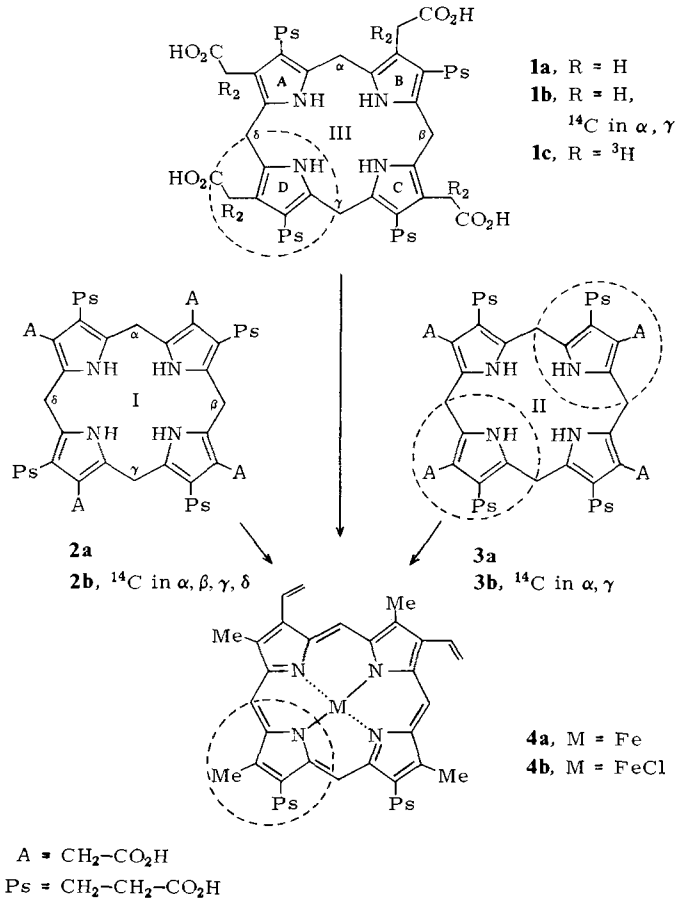
Heme Biosynthesis from Isomeric Uroporphyrinogens**

By *Burchard Franck**, *Wilfried Bock*, and *Udo Wolters*

Uroporphyrinogen III, **1a**, is precursor and key building block[1] in the biosynthesis of the blood pigment heme **4a**[2], as well as of related biologically active tetrapyrroles[3]. Of the three other **1a**-isomers, which differ from each other by "inversion" of the pyrrole rings (in dotted circles), only uroporphyrinogen I, **2a**, has been found in nature. Since uroporphyrinogen I, the red dehydration product of **2a**, is deposited in all organs with pathological disorders of heme biosynthesis (porphyrias) it has been assumed that **2a** is not a biosynthetic precursor of **4a**[4]. We have now found that uroporphyrinogen I, **2a**, and even II, **3a**, can be converted enzymically into heme **4a**.



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[**] Tetrapyrrole Biosynthesis, Part 15.—Part 14: G. Bringmann, B. Franck, *Liebigs Ann. Chem.*, in press.

Hemolyzed duck blood served as the enzyme system for the incorporation experiments. In order to enable reliable statements to be made, the starting materials were dimensioned to correspond to amounts of product in the mmole region. ^{14}C- and ^{3}H-labeled uroporphyrinogens I, **2b**, II, **3b**, III, **1b**, and **1c** were obtained by total syntheses involving 15—22 steps. Selective ^{3}H-labeling of **1c** was performed using $[Mg(py)_6]I_2/^{3}H_2O$.

In order to be able to compare the incorporation of the isomeric uroporphyrinogens unimpaired from variations in enzyme activity, they were "fed" as pairs, one component of which was labeled with ^{14}C, the other with ^{3}H, to the enzyme system. Final ^{14}C- and ^{3}H-determination of the heme **4b**, which was isolated from these competition experiments and purified to constant radioactivity gave the incorporation values of the uroporphyrinogens (Table 1).

Table 1. Competitive incorporation of the isomeric uroporphyrinogens (Uro'gens) III, **1b**, **1c**, I, **2b**, and II, **3b** into heme **4b** over 48 h.

Experiment	Precursor	Radioactivity [nCi] Precursor	4b	Incorp. [%]
1	^{14}C-Uro'gen III **1b**	360	34.5	9.6
	^{3}H-Uro'gen III **1c**	750	23	3.1
2	^{14}C-Uro'gen I **2b**	1920	56.6	2.9
	^{3}H-Uro'gen III **1c**	910	32.8	11.2 [a]
3	^{14}C-Uro'gen II **3b**	610	10.2	1.7
	^{3}H-Uro'gen III **1c**	920	37.3	12.6 [a]

[a] Corrected with the tritium-loss factor from the experiment No. 1 (=3.10).

The uroporphyrinogens I, **2**, and II, **3**, which previously had not been considered as heme precursors, exhibit significant incorporation values of 2.9 and 1.7%, respectively, which are only smaller than those of uroporphyrinogen III, **1**, by a factor of 4 to 7. Presumably, inversion of the pyrrole nuclei D and B, respectively, occurs in the enzymic conversions of **2** and **3** into the blood pigment heme **4a**.

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Antimony Homologues of Dinitrogen and Azobenzene as Complex Ligands: Preparation and Structure of $[Sb{\equiv}Sb\{W(CO)_5\}_3]$ and $[PhSb{=}SbPh\{W(CO)_5\}_3]$**

By *Gottfried Huttner**, *Ute Weber*, *Beate Sigwarth*, and *Olaf Scheidsteger*

The homologue of dinitrogen :Sb≡Sb: is capable of existence only at high temperatures in the gas phase; simi-

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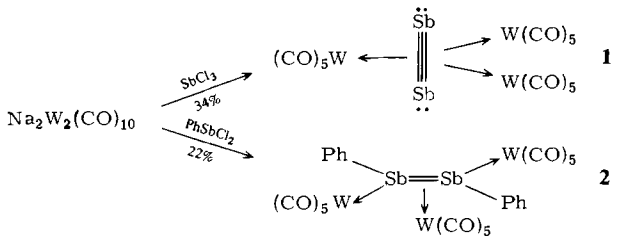
larly the homologue of azobenzene Ph—Sb=Sb—Ph is not stable as the monomeric molecule in the free state.

These reactive species have now been stabilized for the first time as complex ligands in the compounds **1** and **2**. The diantimony complex **1** is formed on reductive dehalogenation of $SbCl_3$ with $Na_2W_2(CO)_{10}$; under the same conditions (tetrahydrofuran, 20 °C; SiO_2, toluene/*n*-pentane as eluent), $PhSbCl_2$ furnishes the "stibobenzene" derivative **2**. Both complexes are obtained in the form of red



crystals (m.p. 140 and 110 °C (dec), respectively) which are stable at 20 °C, even on exposure to air. Their composition is secured by elemental analysis and spectroscopic data, their structure by X-ray structure analyses (Fig. 1).

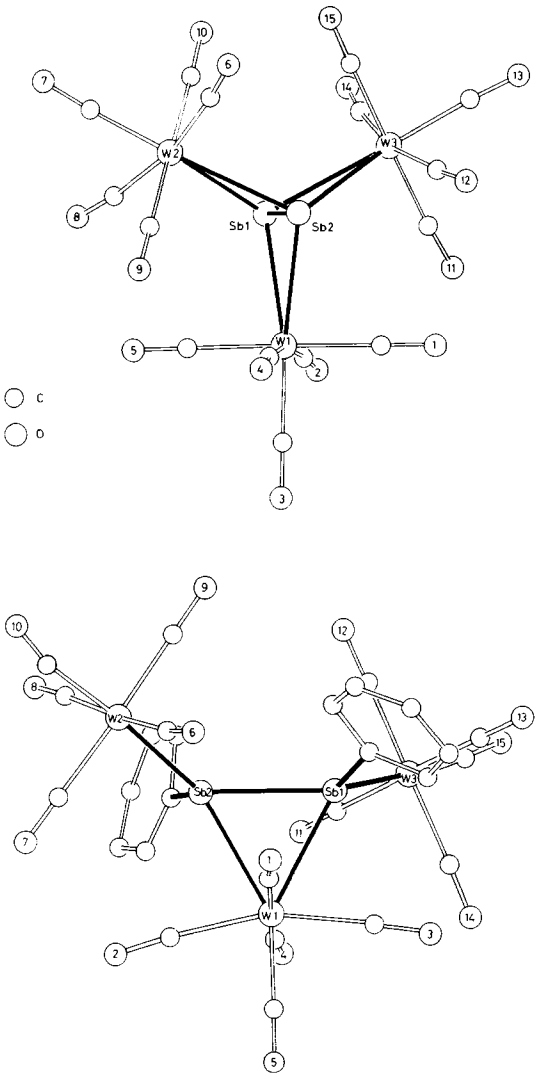


Fig. 1. Structures of the new complexes **1** (top) and **2** (bottom) in the crystal.

In the star-shaped diantimony complex **1** the Sb_2-dumbbell forms the axis of an Sb_2W_3 skeleton with idealized D_{3h} symmetry. All three bonding electron pairs of the Sb≡≡Sb ligand are coordinatively active and bind a total of three $W(CO)_5$ moieties. We recently observed and analyzed this novel bonding behavior, in which an N_2-homologous ligand is coordinated "side-on" as 6e donor to three 16e fragments, for the first time for the molecule $[As{\equiv}As\{W(CO)_5\}_3]$ homologous to **1**[6]. Despite lengthening by the coordinative interaction, the Sb—Sb distance in the diantimony ligand with a length of 266.3 pm is about 20 pm shorter than the Sb—Sb single bond[1b]. A similarly short Sb—Sb distance is found in **2**, in which the azobenzene-homologous PhSb=SbPh is coordinated *via* both free electron pairs as σ-ligand and *via* the double bond as π-ligand. While similar forms of coordination have already been observed previously for "arsenobenzene"[5b], **2** is the first example of a complex-stabilized "stibobenzene".

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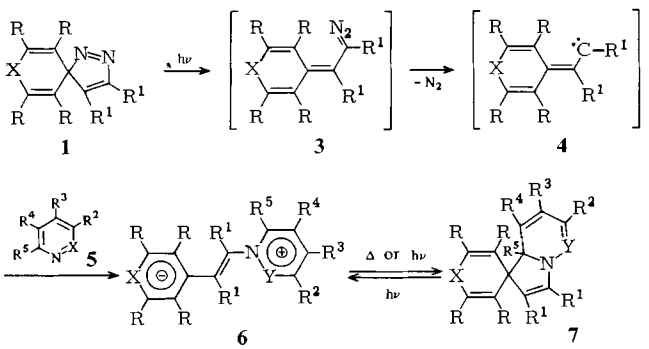
Novel Synthesis of Spiro[1,8a]dihydroindolizines; A New Photochemically Reversible System**

By *Hubert Gross* and *Heinz Dürr**

Photochromic systems are of interest, *inter alia*, in silver-free photography, in data storage[1a,c], and as potential solar energy conversion systems[2]. Photochromic systems based on spiro[1,8a]dihydroindolizines **7** are well known[3].

We report here on a novel synthesis of **7**, which does not require the use of spirocyclopropenes and which for the first time can also be carried out with thermally labile[4] as well as CN- or CF_3-substituted[3b] spiro-3H-pyrazoles **1**. The new systems **6a/7a** and **6b/7b** are photochemically reversible ("photochemically switchable").

Irradiation of a solution of **1** in **5**, or more advantageously of **1** dissolved in a 1% etheral solution of **5** (HPK/125 W lamp, Pyrex filter) affords **7** in moderate to very good yields (see Table 1). Intermediates formed in the pho-



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tochemical reaction could be **3**, **4**, and the betaine **6**, which cyclizes to **7** on warming.

Table 1. (Selected data). Some data of the spiro[1,8a]dihydroindolizines **7** and betaines **6**. R^2 to R^5 = H; R—R = $(CH{=}CH)_2$. ΔG^{+} (**6a**→**7a**) = 23.4 kcal/mol, ΔG^{+} (**6b**→**7b**) = 22.4 kcal/mol.

	X [a]	R^1	Y	Yield [%]	7 λ_{max} [nm]	7 $\varepsilon \times 10^3$	6 λ_{max} [nm]	6 $\varepsilon \times 10^4$
a	—	CN	CH	68	410	6.7	560	3.3
b	—	CN	N	47	395	9.9	535	3.2
h	—	CF_3	CH	47	327	0.34	[c]	
j	—	CF_3	N	79	362	0.34	[c]	
k	CO	CN	CH	47	418	5.2	[c]	
n	S	[b]	CH	26	376	9.1	500	0.36
p	CH_2CH_2	[b, d]	CH	62	390	9.7	510	0.1

[a] A dash signifies no bridge. [b] $R^1 = CO_2CH_3$. [c] Not measureable at room temperature. [d] **6p** and **7p** contain an annelated benzene ring:

The UV maxima of **7a**—**q** lie between 327 and 440 nm, those of **6a**—**q** between 500 and 726 nm. The halflife times of **6** bearing CN substituents are up to 54 h.

We observed that the deep-red betaines **6a** and **6b** can be photochemically discolored and that the resulting yellow products are identical with **7a** and **7b**, respectively. These compounds thus constitute the first photochemically reversible dihydroindolizine systems. The degree of conversion **7**→**6** is 94%. The photoreversibility is somewhat suppressed by O_2[8].

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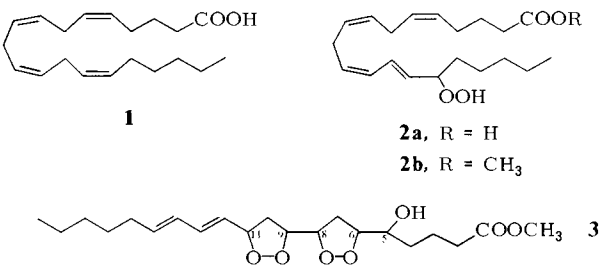
Serial Cyclizations of An Arachidonic Acid Hydroperoxide

By *Jamil A. Khan* and *Ned A. Porter**

The mechanistic pathways involved in the free radical autoxidation of polyunsaturated fatty acids and esters have not been fully elucidated. Autoxidation of 5,8,11,14-eicosatetraenoic acid (arachidonic acid) **1**, for example, leads not only to the biologically important[1] hydroperoxy eicosatetraenoic acids (HPETE) **2a**[1a], but also to cyclic peroxides (dioxolanes) that may have some biological significance.

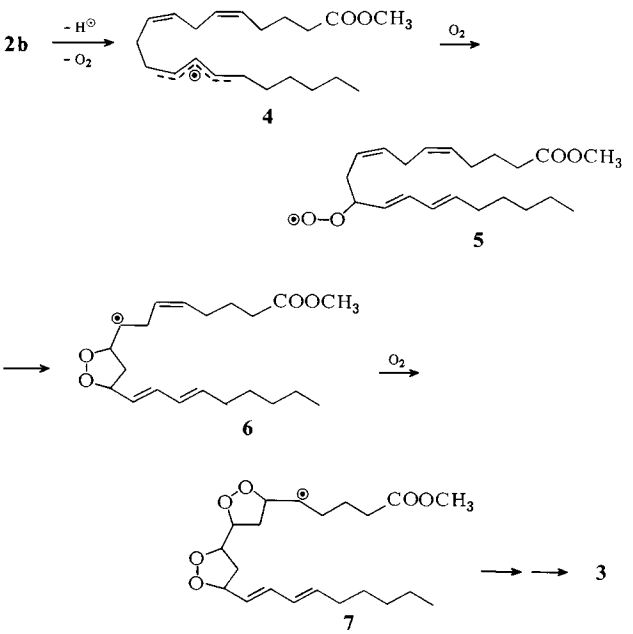
We have studied the free radical oxidation of methyl 15-hydroperoxy eicosatetraeonate (15-HPETE) **2b**, and report here on the isolation of the bisdioxolanes **3** formed in this reaction. Isolation of the polycyclic peroxides **3** from **2b** establishes the importance of β-scission of peroxyl radicals and serial cyclization in the oxidation of polyunsaturated fatty acids[1b, 15].

The autoxidation of **2b** was studied by leaving a solution of **2b** in the presence of di-*tert*-butyl hyponitrite for *ca.* 30 h under oxygen at room temperature.



The resulting product mixture was treated with polymer-bound triphenylphosphane to reduce any hydroperoxide functionality to hydroxide. The six most polar diastereomeric peroxides **3** were isolated by high-pressure liquid chromatography in 5—10% yield. The ^{1}H-NMR and UV spectra showed that these compounds are conjugated dienes and all had (*E,E*) configurations, suggesting the presence of two dioxolane rings and a secondary hydroxy group. The structural assignments followed from a mass spectroscopic analysis of the compounds formed after reduction to polyols by H_2/Pd and their subsequent silylation.

Since hydroperoxides are precursors of peroxyl radicals[15], and β-scission has been proposed to account for the product distribution in the autoxidation of linoleic and arachidonic acids[16], the mechanism shown in Scheme 1 could account for the formation of **3** from **2b**.



Scheme 1.

The formation of only six of the 16 possible diastereomers of **3** in the oxidation of **2b** suggests some stereoselectivity in the cyclization leading to **3**. In particular, the for-

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mation of *cis*-3,5-disubstituted 1,2-dioxolanes is strongly favored[9, 15]. Only four diastereomers of **3**, however, could be *cis*-substituted on both dioxolane rings. While we cannot unambiguously assign structures to all diastereomers, comparison of ^{1}H-NMR spectroscopic data from **3** with that of other dioxolanes[17] suggests that four of the six products are *cis*-substituted on both dioxolane rings, while the remaining two isomers have one *cis*- and one *trans*-substituted dioxolane ring.

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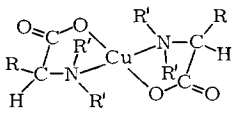
Resolution of D- and L-Amino Acids by HPLC using Copper Complexes of *N,N*-Dialkyl-α-amino Acids as Novel Chiral Additives

By *Shulamith Weinstein**

We report the separation of α-amino acid enantiomers by reversed phase high performance liquid chromatography (HPLC), using Cu^{II} complexes of *N,N*-dialkyl-α-amino acids **1** as chiral additives to the mobile phase. The



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N,N-dialkyl groups were systematically varied to evaluate the influence of structural features on chiral differentiation, and hence contribute to the understanding of the technique and widen its scope. The work is based on the method of *Hare* and *Gil-Av*[1, 2], who resolved α-amino acids using the Cu^{II}-L-proline complex.

The stereoselectivity in the system stems from the difference in equilibrium constants for ligand exchange between the chiral additive CuL_2 (L is ligand of L-configuration) and the L′ and D′ molecules (L′ and D′ are L- and D-enantiomers, respectively) of the substrate undergoing resolution:

$$CuL_2 + L' \rightleftharpoons CuLL' + L \qquad CuL_2 + D' \rightleftharpoons CuLD' + L$$

Ligand exchange may occur in the aqueous mobile phase or on the stationary phase, which resembles an organic solvent by virtue of its long chain (C_{18}) molecules. The ligands L were constructed such that the number of *cis-trans* and conformational isomers of the square-planar complex be limited, and that its lipophilicity (for interaction with the stationary phase) could be gradually modified. *N,N*-dialkylamino acids fulfil these requirements. In addition, inspection of molecular models indicates that the ternary diastereomeric complexes of Cu^{II}, *N,N*-dialkylamino acid, and amino acid are also crowded molecules, reducing the number of possible isomers.

The following amino acid derivatives were prepared, converted into their copper(II) complexes **1**, and these added to the mobile phase for the HPLC separation:

$R'_2N—CHR—COOH$
$R = CH_3$ (alanine), $CH(CH_3)_2$ (valine)
$R' = CH_3$, C_2H_5, n-C_3H_7, n-C_4H_9, n-C_5H_{11}

Good resolutions were obtained e.g. the ratio of the elution times for the separation of L- and D-valine (62.1 and 11.0 min, respectively) using the Cu^{II} complex of *N,N*-dimethyl-L-valine is 5.65 and that of L- and D-glutamic acid using the Cu^{II} complex of *N,N*-di-*n*-propyl-L-alanine is 1.80. Relatively small variations in the length of the *N*-alkyl group strongly influence the stereoselectivity, whereas alanine and valine derivatives which had appreciably different α-carbon substituents but the same *N*-substituents were resolved to a similar extent. Using a given chiral eluent, the same order of elution for the enantiomers was observed for all the amino acids investigated (except for histidine). This indicates that for a given ligand L, the ternary complexes, CuLL′ and CuLD′ probably have a similar structure, and that the relative stabilities of CuLL′ to CuLD′ are the same for all the α-amino acid ternary complexes. The elution order of the enantiomers of all the amino acids is reversed when *N,N*-diethyl complexes are added to the eluent. This emphasizes the role played by the N atom coordinated to the metal. Because of the requirement for planarity in Cu^{II} complexes, and the high steric bulk around the alkylated nitrogen, small changes in structure and conformation in the coordination sphere produce a large effect on the selectivity in forming diastereomeric species.

The anomalous order of elution observed with the enantiomers of histidine in presence of the *N,N*-dimethyl- and *N,N*-diethyl-complexes of both alanine and valine is probably due to coordination of the imidazole nitrogen to Cu^{II}. With higher alkylated derivatives in the eluent, coordination of the imidazole nitrogen is sterically less favored, and "normal" elution occurs.

The fraction of complex **1** adsorbed on the stationary phase is greater than that in the aqueous phase. Furthermore, stability constants of copper(II)-amino acid complexes were found to be higher in organic solvents than in aqueous solution[8]. Thus, a higher percentage of diastereomeric species—upon which selectivity depends—is found in the stationary phase, supporting the view that chiral differentiation depends mainly on interactions with species adsorbed on the stationary phase.

The novel complexes **1** thus extend the scope of the method described by *Hare* and *Gil-Av*[1, 2]. The Cu^{II} complex of *N,N*-di-*n*-propyl-L-alanine, resolves *all the enantiomers of the protein amino acids* (with the exception of cysteine, resolved as cysteic acid)[14]. Problems of peak overlap of various amino acids can be solved by varying the *N,N*-dialkylamino acids, and/or by modifying the chromatographic conditions.

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A Branched Chain of Seven Neutral Iodine Molecules in Crystalline Bis(dithizone)hepta(diiodine)**

By *Frank H. Herbstein** and *Willi Schwotzer*

Dedicated to Professor David Ginsburg on the occasion of his 60th birthday

Although oligomeric chains of iodine and iodide moieties (specifically I^-, I_2, I_3^-) are quite common among polyiodide anions[1] (the largest example known is the S-shaped ion I_{16}^{4-} ($I_3^- \cdot I_2 \cdot I_3^- \cdot I_3^- \cdot I_2 \cdot I_3^-$) found in crystalline (theobromine)$_2 \cdot H_2I_8$[2a]), only one oligomeric polyiodine cation is known (I_{15}^{3+} in $I_5^+SbF_6^-$[2b]), and only one compound containing a chain of neutral iodine molecules (bis(triphenylphosphane sulphide diiodine) diiodine[2c], in which an $(I_2)_3$-chain is anchored at its two ends by sulfur atoms).

We have now found that a mixture of dithizone and iodine (1 : 4) refluxed in $CHCl_3$ gives black needles of composition (dithizone)$_2(I_2)_7$ **1** on cooling. The known compound dithizone$\cdot I_2$[3] is obtained if a 1 : 1 molar ratio is used.

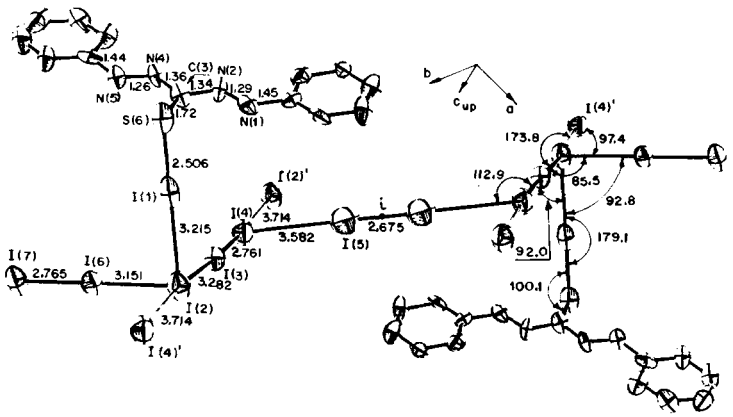
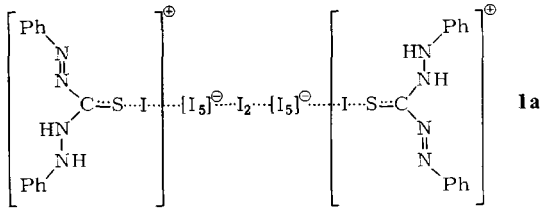


Fig. 1. Structure of **1** in the crystal. Standard deviations <0.005 Å (I—I), <0.04 Å (C—N, C—C), ≈0.1° (∢III).—**1** forms triclinic crystals, $a = 13.212(8)$, $b = 10.137(7)$, $c = 9.746(6)$ Å, $\alpha = 101.8(1)$, $\beta = 87.1(1)$, $\gamma = 109.4(1)°$, $Z = 1$, $P\bar{1}$; $Mo_{K\alpha}$ irradiation, solved using Patterson and direct methods (MULTAN 77), refined to $R = 8.6\%$ with 2916 reflections in the final refinement cycle. I(2)', I(4)', and the corresponding atoms in the other molecular half belong to neighboring molecules.

The centrosymmetric molecules **1** (Fig. 1) contain nonplanar $(I_2)_5$-chains anchored at both ends by sulfur atoms; furthermore the iodine chain is branched by bonding of two additional iodine molecules at I(2) and I(2'). The bond lengths and bond angles suggest that **1a** contributes significantly to the overall resonance hybrid.



1a

The I_5^- units have dimensions similar to those found in the discrete V-shaped pentaiodide ions of bis(potassium valinomycin)pentaiodide triiodide[4a] and the interacting V-shaped pentaiodide ions of tetramethylammonium pentaiodide[4b]. The CS distances in **1** (1.722(10) Å) are about the same as those in the CT-compound *N*-methylthiocaprolactam iodine[5a] (1.716(5) Å), and the SI distances in **1** (2.506(8) Å) are shorter than in the comparable compound (2.688(2) Å). Nevertheless the S-bound iodine moieties in **1** are not to be interpreted as true cations, for these would be expected to pack as separate units in the crystal structure (cf. [5b]). This description of the bonding in the iodine chain can only be a first approximation; the distances between the I atoms of neighboring molecules are only 3.714(3) Å.

The dithizone moieties have an *anti-s-trans* conformation as do other dithizone derivatives. Unfortunately, the bond lengths in the dithizone moiety are not accurate enough to allow conclusions to be drawn about the intramolecular bonding or tautomerism. H atoms bonded to nitrogen could not be detected in difference maps.

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Ph(Me$_3$Si)C=PCl as Educt for Methylenephosphanes with Alkyl-, Amino-, Phosphino-, Alkoxy-, or Alkylthio-Groups on Phosphorus**

By *Rolf Appel** and *Ursula Kündgen*

Dedicated to Professor Herbert Grünewald on the occasion of his 60th birthday

Until now only compounds of two coordinated triply bonded phosphorus with doubly bonded nitrogen, phosphorus, and carbon were known[10]. In contrast to iminophosphanes[6, 7], as well as phosphandiyl-[8] and phosphorandiylphosphanes[9], methylenephosphane compounds with P—H, P—Si, and P—halogen bonds[5] have also been synthesized; acyclic *P*-phosphino, -alkoxy- and -alkylthio derivatives have, however, not been prepared.

We have now found that the *P*-chloro(methylene)phosphane **1**[5] is highly suitable for the preparation of the novel phosphanes **2**—**6** with X—P=C part structures (X = C, N, P, O, S).

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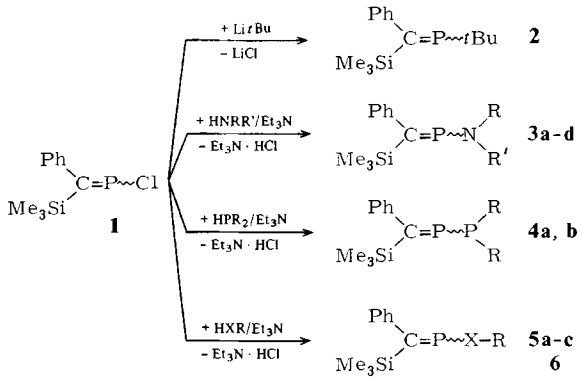
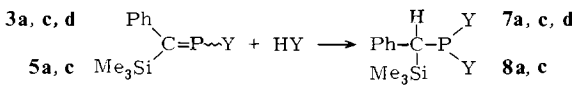
[**] Low Coordinated Phosphorus Compounds, Part 7. This work was supported by the Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen and by the Deutsche Forschungsgemeinschaft. Part 6: R. Appel, A. Westerhaus, *Tetrahedron Lett. 1981*, 2159.



3a, R = R′ = Me
3b, R = R′ = *i*Pr
3c, R, R′ = —$(CH_2)_5$—
3d, R = Me, R′ = Ph
4a, R = *t*Bu
4b, R = Ph
5a, X = O, R = Me
5b, X = O, R = *t*Bu
5c, X = O, R = Ph
6, X = S, R = *n*Bu

The yields of **3a, c, d** and **5a, c** are reduced by nucleophilic addition to the PC double bond of the products. The homogeneity and constitution of the distillatively purified



3, 7, Y = NRR′; **5, 8**, Y = OR

thermostable methylenephosphanes **2—6** were verified by correct elemental analysis, relative molecular masses, and the deshielding in the $^{31}P\{^1H\}$-NMR spectra, as well as by the coupling constant data and low-field position of the methylene C signal in the ^{13}C-NMR spectrum. **3b** and **4a** occur as *E*-isomers. The lone pairs of the diphosphane moiety of **4a** are *trans*-orientated (X-ray structure analysis)[10].

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Macrocycles of D- and L-Proline Residues**

By *Manfred Rothe** and *Werner Mästle*

Dedicated to Professor Leopold Horner on the occasion of his 70th birthday

Peptides containing consecutive proline residues are considerably restricted in their conformational flexibility because of the relatively rigid pyrrolidine rings and strong steric interactions with their neighboring proline residues. Linear oligoprolines with D- and L-structural units are therefore excellent examples for demonstrating the influence of conformation and configuration on the ring closure of a chain.

We have now synthesized for the first time macrocyclic peptides with up to 24 L- and D-proline residues by cyclooligomerization of activated triproline esters. A series of cyclic oligotripeptides *c*-(D-Pro-L-Pro-L-Pro)$_n$ with $n = 1$—8 was obtained, and their ring sizes were determined by MS and GPC (Table 1). *c*-(D-Pro-L-Pro-L-Pro) is the first cyclotripeptide which is present exclusively in the boat conformation, both in the crystal and in solution[4].

Table 1. Cyclopeptides *c*-(D-Pro-L-Pro-L-Pro)$_n$ [a].

n	M.p. [°C]	$[\alpha]_D^{22}$ [b]	V_e [mL] [c]	M^+ (found)
1	181—184	+ 70.7	800	291.15816
2	304	− 60.9	596	582.31660
3	230 (dec.)	−114.5	549	873.47489
4	250 (dec.)	− 72.0	492	1164.63319
5	250 (dec.)	−101.8	462	1455; $(M+Na)^+$

[a] Lyophilized products from water. [b] $c = 1$, H_2O. [c] Elution volumes (GPC, Sephadex LH 20).

Furthermore, we were also able to synthesize the alternating L,D-cyclohexapeptide *c*-(L-Pro-D-Pro)$_3$, for which a highly selective complexation of cations has been postulated[2] (26%, dec. >310 °C).

Tripeptides with CONH-groups in principle undergo cyclodimerization to give cyclohexapeptides; however, no larger rings than *c*-triprolyl are formed during ring closure of *all*-L-triproline even at higher concentrations. This can be attributed to the fact that, according to NMR findings, linear oligo-L-prolines already from $n = 3$ onwards have relatively rigid helical structures with spatially fixed terminal groups, and therefore cannot cyclize. The incorporation of D-proline alters the spatial orientation of the peptide chain. Due to the bridging of the N—C_α bond in the proline the configuration at C_α has a very much stronger influence on the backbone conformation of the peptide chain than in the "usual" amino acids of different chirality.

On ring closure of the diastereomeric L,D-triproline derivatives, each of which give identical cyclopeptides of definite ring size, drastically different cyclization tendencies

Table 2. Cyclization of diastereomeric triproline-2,4,5-trichlorophenyl esters to *c*-(D-Pro-L-Pro-L-Pro)$_n$.

Starting sequence [a]	Overall yield [%]	DOP [%] [b]	$n = 1$	2	3	4	5
			Yield [%]				
$c \ll 0.001$ mol/L in pyridine							
D L L	81	1	78.3	2.5	—	—	—
L D L	57	1.6	3.2	51.7	—	—	—
L L D	54	20.1	30.8	3.5	—	—	—
$c = 0.1$ mol/L in dimethylformamide/triethylamine							
D L L	60	1	5.5	4.1	22.0	11.6	5.7 [c]
L D L	78	—	—	70.5	4.6	3.2	< 1
L L D	74	5.4	4.9	29.0	17.2	7.1	4.7 [c]

[a] Configuration sequence in educt. [b] *N*-terminal dioxopiperazine cleavage. [c] Also larger rings up to $n = 8$.

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were established depending on the configuration sequence and the reaction conditions (see Table 2).

Model considerations reveal that the terminal groups of the linear triproline derivatives containing *cis*-peptide bonds, which are required for ring closure to the cyclotripeptide, are present in a quasi-"cisoid" (L,L,L- and D,L,L-sequence) or quasi-"transoid" (L,D,L- and L,L,D-sequence) arrangement with respect to the less flexible peptide backbones. This leads to a greatly varying distance between the chain ends and thus to a very different tendency to undergo ring closure.

Thus, on using diastereomeric triprolines a very striking example has been discovered for demonstrating the dependence on sequence of the cyclization of linear peptides forming identical cyclopeptides[8]. This dependence on sequence is based on the different conformation of the educt chains due to changes in the α-carbon configuration.

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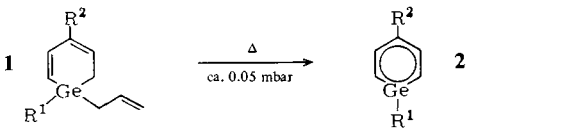
1,4-Dialkylgermabenzenes-Generation and Detection in the Gas Phase**

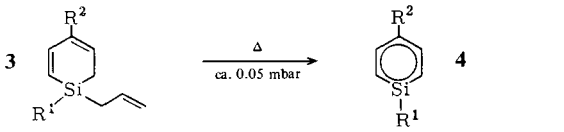
By *Gottfried Märkl, Dieter Rudnick, Reinhard Schulz,* and *Armin Schweig**

We report here on the first, direct spectroscopic detection of 1,4-dialkylated germabenzenes in the gas phase by VTPES (variable temperature photoelectron spectroscopy) experiments[3a, 4a].

The germabenzene and silabenzene derivatives, **2** and **4** respectively, were generated from the allylcyclohexadienes **1** and **3** by gas-phase pyrolysis (450–550 °C, *ca.* 0.05 mbar) according to the method of *Barton et al.*[6a, b]. Since only partial conversions (exception: **3b**→**4b**) can be achieved in these reactions the PE spectra of the compounds **2** and **4** in the region of their two ionization bands (7–9.5 eV) were obtained from the product and educt spectra by subtraction.



a, $R^1 = CH_3$, $R^2 = C(CH_3)_3$; **b**, $R^1 = CH_3$, $R^2 = C_2H_5$; **c**, $R^1 = CH_3$, $R^2 = CH(CH_3)_2$



a, $R^1 = CH_3$, $R^2 = C(CH_3)_3$; **b**, $R^1 = R^2 = CH_3$; **c**, $R^1 = H$, $R^2 = C(CH_3)_3$

That the germabenzene derivatives **2** are actually formed during thermolysis of **1** follows from the good agreement of the vertical ionization energies of germa- and the correspondingly substituted silabenzene derivatives (Fig. 4).

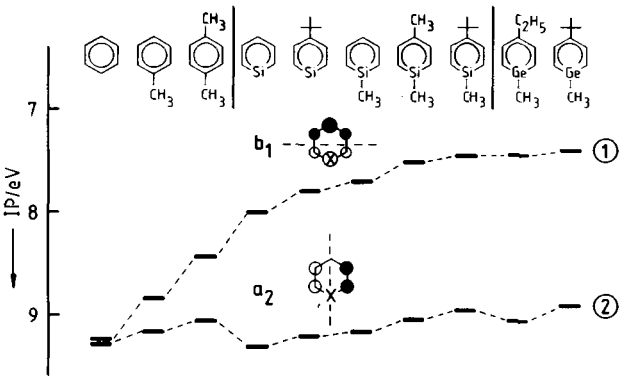


Fig. 4. Vertical ionization energies (IP) ($^2B_1(\pi)$ ① and $^2A_2(\pi)$ ②) of benzene-, silabenzene-, and germabenzene-derivatives. The data for unsubstituted silabenzene and for 1-methyl-1-silabenzene were taken from the literature ([7b] and [6c], respectively).

This agreement is not surprising, since the atomic ionization energies of silicon (8.15 eV) and germanium (7.88 eV) differ only slightly.

From these results we can expect the two first ionizations of the unsubstituted germabenzene to be at 7.95 [$^2B_1(\pi)$] and 9.25 eV [$^2A_2(\pi)$].

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[**] Theory and Application of Photoelectron Spectroscopy, Part 95. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 94: G. Gross, R. Schulz, A. Schweig, C. Wentrup, *Angew. Chem. 93* (1981) 1078; *Angew. Chem. Int. Ed. Engl. 20* (1981) 1021.

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Stereo- and Regioselective Synthesis of Enantiomerically Pure (+)- and (−)-Hexahydrocannabinol by Intramolecular Cycloaddition**

By *Lutz-F. Tietze**, *Günter von Kiedrowski,* and *Bernhard Berger*

The non-natural hexahydrocannabinol (HHC) **4** belongs to the psychotropic cannabinoids; the (−)-(9*R*)-

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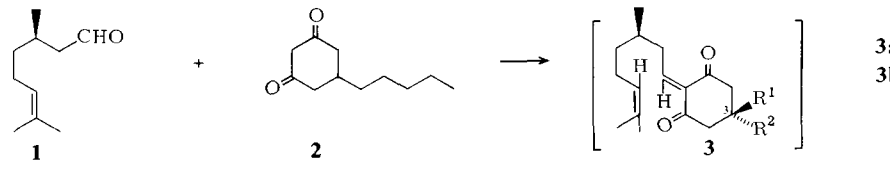
epimer **4a** is almost as active as the natural Δ^8-tetrahydrocannabinol (Δ^8-THC) (**4**, $C^8{=}C^9$), whereas the (9*S*)-epimer **4b** is twenty times less active[1]. Until now, **4** has been synthesized by hydrogenation of Δ^8-THC or Δ^9-THC (**4**, $C^9{=}C^{10}$) resulting in formation of a mixture of both epimers **4a** and **4b**, which are, however, difficult to separate[1].

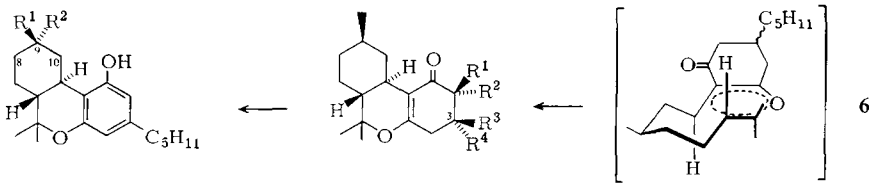
We describe a highly selective synthesis of **4a** and its enantiomer, the key step of which is a stereocontrolled intramolecular Diels-Alder reaction with inverse electron demand.

Condensation of (*R*)-citronellal **1** with 5-*n*-pentyl-1,3-cyclohexanedione[2] **2** at 100 °C in dimethylformamide (DMF) led *via* **3** to a *ca.* 1:2 mixture of both tricyclic pyran derivatives **5a** and **5b**[3] in 65% yield.

The cycloaddition, which presumably proceeds *via* the transition state **6**, is 100% stereocontrolled by the chiral center of citronellal **1**[4]. Formation of both epimeric C-3 compounds can be ascribed to the low stereoselectivity of the aldol condensation (**1**+**2**→**3a**+**3b**). This has, however, no significance for the synthesis of (−)-(9*R*)-HHC **4a**, since C-3 becomes achiral in the subsequent aromatization step.



3a, R^1 = H, R^2 = C_5H_{11}
3b, R^1 = C_5H_{11}, R^2 = H



4a, R^1 = CH_3, R^2 = H
4b, R^1 = H, R^2 = CH_3

5a {R^1 = R^2 = R^4 = H, R^3 = C_5H_{11}}
5b {R^1 = R^2 = R^3 = H, R^4 = C_5H_{11}}
5c {R^1 = SePh, R^2 = R^4 = H, R^3 = C_5H_{11}}
5d {R^1 = R^3 = H, R^2 = SePh, R^4 = C_5H_{11}}

For aromatization, the mixture **5a/5b** is deprotonated by lithium diisopropylamide and converted in 65% yield by phenylselenyl chloride into the selenides **5c** and **5d**, which can be separated by chromatography on silica gel. Oxidation of **5c** and **5d** with *m*-chloroperbenzoic acid at −40 °C to the selenium oxides and subsequent warming up to 25 °C gives, *via syn*-elimination and 1,5-hydrogen shift, the (−)-(3*R*)-HHC **4a**[5] in 70 and 56% yield, respectively. In the elimination step, 3,5-dimethoxyaniline is added to trap the phenylselenenic acid formed (see Part 3). Conversion of **5a/5b** into **4a** can also be carried out as a "one-pot" reaction without isolation of the selenides.

(+)-(9*S*)-HHC (enantiomer of **4a**) can be synthesized in this way using (*S*)-citronellal, which is also commercially available.

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[3] A solution of 1.0 mol equiv. of **2** in anhydrous DMF was added dropwise to 1.5 mol equiv. of **1** (Fluka, 85–90%) in DMF at 100 °C. **5a/5b**: ^{1}H-NMR ($CDCl_3$): δ = 0.42 (q, J = 12 Hz; 0.7 H, 10β-H), 0.46 (q, J = 12 Hz, 0.3 H, 10β-H), 0.84 (t, J = 6 Hz; 3 H, CH_2—CH_3), 0.86 (d, J = 6.5 Hz; 3 H, 9-CH_3), 1.00 (s; 0.3·3 H, 6α-CH_3), 1.02 (s; 0.7·3 H, 6α-CH_3), 1.30 (s, 3 H, 6β-CH_3), 0.9–2.5 (m; 20 H), 2.80 (dm, J = 12 Hz; 0.3 H, 10α-H), 2.84 (dm, J = 12 Hz, 0.7 H, 10α-H).
[4] L.-F. Tietze, G. von Kiedrowski, K. Harms, W. Clegg, G. Sheldrick, *Angew. Chem.* 92 (1980) 130; *Angew. Chem. Int. Ed. Engl.* 19 (1980) 134.
[5] **4a**: oil; R_F = 0.32 (silica gel, ether/petroleum ether = 1/7.5); $[\alpha]_D^{25}$ = −93.6° (c = 0.7 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ = 0.85 (t, J = 7 Hz; 3 H, CH_2—CH_3), 0.93 (d, J = 6.5 Hz; 3 H, 9-CH_3), 1.05 (s; 3 H, 6α-CH_3), 1.36 (s; 3 H, 6β-CH_3), 0.73–1.93 (m; 13 H), 2.42 (t, J = 7 Hz; 2 H, Aryl—CH_2), 2.37–2.55 (m; 1 H, 10a-H), 3.04 (dm; J = 11.5 Hz; 1 H, 10α-H), 4.83 (s; 1 H, OH), 6.08 (d; J = 1.7 Hz; 1 H, 2-H), 6.25 (d, J = 1.7 Hz, 1 H, 4-H).
[6] L.-F. Tietze, G. von Kiedrowski, B. Berger, *Tetrahedron Lett.* 23 (1982), 51.

BOOK REVIEWS

Gas-Phase Reactions. By *V. N. Kondratiev* and *E. E. Nikitin*. Springer-Verlag, Berlin 1980. xiv, 241 pages, bound, DM 118.00.

V. N. Kondratiev, who died recently, and *E. E. Nikitin* are not just scientists who have made fundamental experimental and theoretical contributions to the knowledge of gas-phase reactions. They are also the authors of extensive books on this subject (*V. N. Kondratiev:* Chemical Kinetics of Gas Reactions, 1964; *E. E. Nikitin:* Theory of Elementary Atomic and Molecular Processes in Gases, 1974). The joint monograph presently in question is not an abridged version or a résumé of their previous books, although certain formal similarities and favorite examples are naturally present. It is an independent review of the subject of gas reactions.

Reaction order, rate lows of complex systems, detection of intermediates such as atoms and radicals, their reactions and macroscopic description are briefly summarized in

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two introductory chapters. The theory of elementary processes, Chapter 3, then provides the microscopic formulation of collision cross section/rate constants, the dynamics of adiabatic and diabatic transitions, several representative examples of energy hypersurfaces, and a summary of the transition state theory. A central theme of theoretical reaction kinetics—energy transfer in collisions—is treated thoroughly in 30 pages in Chapter 4. For translation (T), rotation (R), and vibration (V), the TR, RT, VT, and VRT processes are discussed, as well as the intermolecular and intramolecular VV processes and the energy transfer in electronically excited particles. A description of unimolecular reactions in theory and experiment follows in Chapter 5, with the keywords strong/weak collisions, high-pressure/low-pressure region, and activation energy. The treatment of recombination reactions follows logically in Chapter 6, where both the radiation and collision stabilization are considered. Chapter 7 gives a summary of bimolecular exchange reactions and the energy relationships observed in them. The fundamentals of photochemical reactions (excitation, fluorescence, sensitized photolysis) are discussed in Chapter 8 and reactions in electrical discharges with examples of the formation of C_2H_2, NH_3, and O_3 in Chapter 9. Chapter 10, written by *V. L. Talroze,* is an authoritative introduction to the field of radiation chemistry, with emphasis on negative ions, ion-molecule and ion-ion recombination reactions, and radiolysis of hydrocarbons, N_2+O_2, and NH_3. Chain reactions are presented in the splendid style of the Russian school *(Semenov)* in Chapter 11, with aspects on homogeneous/heterogeneous chain initiation, chain branching, induction period, influence of radiation and the examples of hydrocarbon $+O_2$, H_2+O_2, and H_2+halogens. The book ends with Chapter 12, a discussion of combustion processes (self-ignition, flames and flame-propagation velocity, detonation).

This presentation of the extensive subject of gas-phase reactions is limited to 225 pages of text, so that derivations, where given, could only be outlined; otherwise the formulas given are interpreted. Not an exceptional teaching book for students, it is nevertheless a compact, well-readable, and impressive presentation of a large subject with particular regard to elementary processes and could therefore win a good place for itself in competition with the many books on gas kinetics. Altogether it is a fine book, excellently made-up for a high price.

K. Hoyermann [NB 536 IE]

Photoacoustics and Photoacoustic Spectroscopy. By *A. Rosencwaig*. Wiley and Sons, Chichester 1980; xii, 309 pages, 139 figs., bound, £ 19.00.

The photoacoustic effect (*Bell* 1880), which until 1973 had been little considered, constitutes the basis of a new spectroscopic method, photoacoustic spectroscopy (PAS), a combination of optical spectroscopy and ultramicrocalorimetry. Its principle is that photons penetrating matter release thermal energy when absorbed and this energy produces pressure fluctuations in the atmosphere surrounding the sample, which can be picked up with a sensitive microphone. Photons that are not absorbed or scattered are photoacoustically inactive. With optically dense samples (*e.g.* powders, amorphous solids, gels, and colloids)—in contrast to conventional optical absorption spectrometry—specific signals from material components are obtained, and also an indication of the thermal and elastic properties of gaseous, liquid, or solid organic and inorganic substances. Among other things, photoacoustics can also be used to measure the thickness of thin layers and films.

The author of this first monograph on the relatively new field of photoacoustics and PAS participated in its pioneering development at Bell Laboratories, Murray Hill, New Jersey, and so this introduction into the theory and practice of the new method could hardly come from a more qualified source.

After a short historical presentation of the photoacoustic effect and PAS (8 pages), the PAS of gases, solids, and liquids is discussed in eleven chapters, in each case from theoretical and experimental aspects (121 pages). Sections then follow on the spectroscopic investigations of solids and liquids (28 pages) and of other matrices (26 pages), on the applications of PAS to the study of catalytic and chemical reactions (7 pages) and to the investigation of surfaces (9 pages), and on its uses in biology (11 pages) and medicine (32 pages). Some specific techniques and uses are dealt with in the last five chapters.

All things considered, the book presents the state of PAS and its various applications up to 1979 in a comprehensive and well arranged form and in easily understandable style.

As is so often observed with pioneers of a new method, the author is very euphoric about PAS. He says very little about the limitations already emerging clearly in practice, such as above all the poor signal resolution, the interference due to self-saturation, and the considerable difficulties with quantification. The reviewer should, therefore, like to warn against an overestimation of the present usefulness of PAS for the solution of problems in applied analysis when the substances to be investigated are more complex than the simple model samples, which are still used exclusively to illustrate the efficiency of the method. As the reviewer sees it, at the present stage of development very little can be said regarding the future of PAS. These critical observations, however, should by no means detract from the value of this introduction into a definitely promising field, which will certainly be gratefully received by people whose interests extend beyond analytical chemistry.

Günther Tölg [NB 537 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 (Federal Republic of Germany).

Handbook of High Resolution Multinuclear NMR. By *C. Brevard* and *P. Granger*. John Wiley & Sons, Chichester 1981. xvii, 229 pp., bound, £ 18.15.—ISBN 0-471-06323-1

Carbon-13 NMR Spectral Problems. By *R. B. Bates* and *W. A. Beavers*. The Humana Press, Clifton, New Jersey 1981. xxi, 259 pp., bound, £ 11.50.—ISBN 0-89063-010-5

Arzneimittelwirkungen. Ein Lehrbuch der Pharmakologie für Pharmazeuten, Chemiker und Biologen. By *E. Mutschler*. Wissenschaftliche Verlagsgesellschaft, Stuttgart 1981. 4th completely revised edition. xvii, 771 pp., bound, DM 68.00.—ISBN 3-8047-0608-8

Kinetics and Mechanism. A Study of Homogeneous Chemical Reactions. By *J. W. Moore* and *R. G. Pearson*. John Wiley & Sons, Chichester 1981. xv, 455 pp., bound, £ 23.70.—ISBN 0-471-03558-0

Modern Fluorescence Spectroscopy. Edited by *E. L. Wehry*. Plenum Press, New York 1981. Vol. 3: xx, 354 pp., bound, $ 39.50.—ISBN 0-306-40690-X. Vol. 4: xvi, 282 pp., bound, $ 35.00.—ISBN 0-306-40691-8

Membrantrennverfahren. Ultrafiltration und Umkehrosmose. By *R. Rautenbach* and *R. Albrecht*. Verlag Salle/Sauerländer, Frankfurt am Main 1981. 230 pp., bound, DM 140.00.—ISBN 3-7935-5507-0

Römpps Chemie-Lexikon. Band 2, Cm-G. By *O. A. Neumüller*. New improved and supplemented eighth edition. Franckh'sche Verlagshandlung, Stuttgart 1981. 749 pp., bound, DM 195.00.—ISBN 3-440-04512-9

Lexikon Biochemie. Edited by *H. D. Jakubke* and *H. Jeschkeit*. 2nd improved edition. Verlag Chemie, Weinheim 1981. 609 pp., bound, DM 40.00.—ISBN 3-527-25904-X

Lecture Notes in Chemistry. Vol. 25: Intermolecular Forces and Their Evaluation by Perturbation Theory. By *P. Arrighini*. Springer-Verlag, Berlin 1981. ix, 243 pp., bound, DM 39.80.—ISBN 3-540-10866-1. **Vol. 26: Lattice Dynamics of Molecular Crystals.** By *S. Califano, V. Schettino*, and *N. Neto*. Springer-Verlag, Berlin 1881. vi, 309 pp., bound, DM 52.50.—ISBN 3-540-10868-8

Modern Hot-Atom Chemistry and Its Applications. By *T. Tominaga* and *E. Tachikawa*. Springer-Verlag, Berlin 1981. viii, 154 pp., bound, DM 98.00.—ISBN 3-540-10715-0

Structure and Bonding 46. Edited by *M. J. Clarke, J. B. Goodenough, P. Hemmerich, J. A. Ibers, C. K. Jørgensen, J. B. Neilands, D. Reinen, R. Weiss*, and *R. J. P. Williams*. Springer-Verlag, Berlin 1981. v, 176 pp., bound, DM 88.00.—ISBN 3-540-10655-3

Topics in Current Chemistry. Edited by *F. L. Boschke*. Springer-Verlag, Berlin 1981. Vol. 17: vii, 165 pp., bound, DM 92.00.—ISBN 3-540-10805-X. Vol. 18: vii, 197 pp., bound, DM 76.00.—ISBN 3-540-10793-2

Bioprozesstechnik. Berechnungsgrundlagen der Reaktionstechnik biokatalytischer Prozesse. By *A. Moser*. Springer-Verlag, Berlin 1981. xv, 198 pp., bound, DM 69.00.—ISBN 3-211-81628-3

Stability and Reactivity of Crown-Ether Complexes. By *F. de Jong* and *D. N. Reihoudt*. Academic Press, London 1981. 163 pp., bound, £ 12.80.—ISBN 0-12-208780-1

Chemical Criminalistics. By *A. Maehly* and *L. Strömberg*. Springer-Verlag, Berlin 1981. vii, 322 pp., bound, DM 162.00.—ISBN 3-540-10723-1

Numerical Methods in the Study of Critical Phenomena. Edited by *J. Della Dora, J. Demongeot*, and *B. Lacolle*. Springer-Verlag, Berlin 1981. ix, 269 pp., bound, DM 60.00.—ISBN 3-540-11009-7

The Environmental Impact of Man's Use of Water. Part 2. Edited by *S. H. Jenkins*. Pergamon Press, New York 1981. p. 265—p. 536, bound, $ 30.00.—ISBN 0-08-028412-4

Advances in Electrochemistry & Electrochemical Engineering. Vol. 12. Edited by *H. Gerischer* and *C. W. Tobias*. John Wiley & Sons, Chichester 1981. x, 361 pp., bound, £ 29.25.—ISBN 0-471-87528-7

Water Vapour Line Parameters From Microwave to Medium Infrared. By *J.-M. Flaud, C. Camy-Peyret*, and *R. A. Toth*. Pergamon Press, New York 1981. 269 pp., bound, $ 75.00.—ISBN 0-08-026181-7

Progress in Polymer Science. Vol. 7: Plastics Engineering. By *R. J. Crawford*. Pergamon Press, New York 1981. 334 pp., bound, $ 75.00.—ISBN 0-08-026262-7

Corrigendum

The following correction should be made to the review article entitled "The Norbornyl Cation: Prototype of a 1,3-Bridged Carbocation" by Cyril A. Grob, *Angew. Chem. Int. Ed. Engl. 21* (1982) 87:

On p. 87, the last sentence of the summary should read: "Bridging is reduced by electron-attracting substituents and by *bridging strain*."

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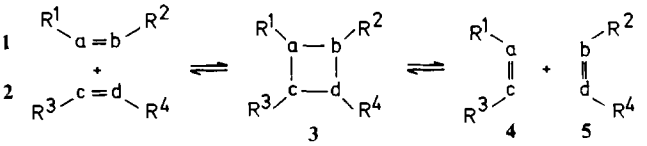
[2 + 2]-Cycloreversions

By Ernst Schaumann* and Roger Ketcham

Four-membered rings can be cleaved thermally, photochemically, or catalytically into two π bonded fragments. Theoretical calculations, kinetic studies, and investigations of stereo- and regioselectivity have been undertaken to clarify the question of whether the reaction involves one or two steps and to permit predictions on its course. [2 + 2]-Cycloreversions have been used to clarify the structure of four-membered rings, to prepare highly reactive π electron-systems and—in combination with a [2 + 2]-cycloaddition—to protect double bonds. The combination of a cycloaddition and -reversion can be used to convert a carbonyl group into an olefin. Starting with compounds containing annelated four-membered rings, compounds with two functional groups or large ring systems can be prepared. [2 + 2]-Cycloreversions have also been discussed in connection with storage of solar energy.

1. Introduction and Definitions

On the heels of the conservation of orbital symmetry rules formulated by *Woodward* and *Hoffmann*[1], cycloaddition chemistry experienced a boom. After significant work on the scope and mechanistic implications, increased interest is now being directed to the preparative uses of the cycloadducts. One aspect of this is the formal reverse of cycloaddition, that is cycloreversion. The synthetic potential of the retro-Diels-Alder reaction[2], 1,3-dipolar cycloreversions[3], and cleavage of three-membered rings[4] have been reviewed. [2 + 2]-Cycloreversions, however, have only been touched on in earlier reviews[5–9]. Here we attempt to review the relevant literature and to organize the material so as to encourage its synthetic application.



We will classify a reaction as a [2 + 2]-cycloreversion only when two opposing σ bonds of a carbo- or heterocyclic four-membered ring **3** are cleaved to give **1/2** or **4/5**. Other terms used in the literature, "retrograde [2 + 2]-cycloaddition", and "[4→2 + 2]-cycloelimination" are synonymous with [2 + 2]-cycloreversion. On the other hand, the concept "metathesis" has come to be used for the disproportionation of alkenes catalyzed by transition-metal compounds (cf. Section 4.1).

If in **1**—**5**, a/d and b/c are identical then the educts and products of the overall reaction of **1/2** to give **4/5** belong to the same chemical type, and only an exchange of substituents occurs. This specific type of cycloaddition and cycloreversion has been called an "exchange reaction" by *Ulrich*[10,11]. The complete reaction often takes place *in situ*

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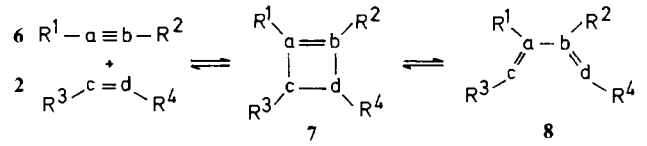
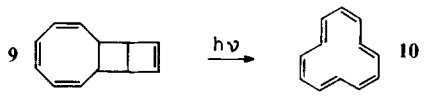
without isolation of the cycloadduct **3**, which is a plausible intermediate.



7 **8**

Starting from an unsaturated four-membered ring **7**, only formation of the fragments **2** and **6** is viewed as a cycloreversion. The electrocyclic ring opening **7**→**8** is not included in the above definition. Electrocyclic reactions will be considered only when they compete with cycloreversion to produce compounds of types **2** and **6**. Furthermore, ring-expansions of four-membered rings, which are annelated at opposite sides by 2n and 2m membered rings with n and m conjugated double bonds, are excluded. Thus, reactions such as conversion of the tricycle **9** into the annulene **10**[12] are better interpreted as a cyclic electron shift in the two outer rings than as a [2+2] cycloreversion of the central ring.

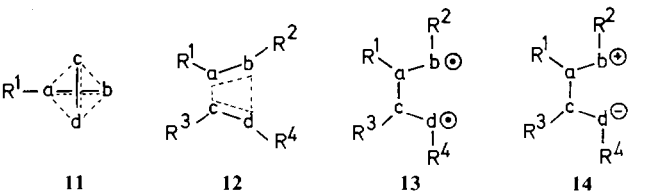


9 **10**

The [2+2]-cycloreversion of 1,2-oxaphosphetanes to give a phosphane oxide and an olefin constitute the last step in the Wittig reaction[13a]. Coverage of π-bond formation *via* phosphorus-containing four-membered rings would exceed the bounds of this review and the reader is therefore referred to the available monographs[13b].

2. Mechanism of [2+2]-Cycloreversions

According to the principle of microscopic reversibility the same considerations for the reaction mechanism must apply to the [2+2]-cycloreversion as to the [2+2]-cycloaddition. If the two σ-bonds are broken simultaneously, then according to the Woodward-Hoffmann rules[1] for a thermally induced cleavage this corresponds to a $[_\sigma 2_s + _\sigma 2_a]$-process having transition state **11** in which the fragments separate from each other in a "corkscrew"[5] motion. A geometrically more favorable $[_\sigma 2_s + _\sigma 2_s]$-reaction path *via* transition state **12**[14] is thermally "forbidden" *i.e.* would be associated with a much higher activation energy. In the case of photochemical [2+2]-cycloreversions the reverse relationships are expected, *i.e.* **12** would be favored over **11**[1].



11 **12** **13** **14**

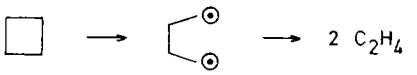
The burden of twisting as in **11** disappears if a two-step process involving successive cleavage of the bonds is assumed. As limiting cases for such an intermediate the 1,4-tetramethylene type diradical **13** and a 1,4-zwitterion **14** must be discussed. Viewed theoretically, **13** and **14** differ only in degree[15]. Heuristically it is useful to favor the diradical **13** for substituents which can stabilize unpaired electrons, and when R^2 is an electron-donor and R^4 an electron-acceptor to couch the discussion in terms of the zwitterion **14**.

Until the mid seventies the literature often reflected a tendency to interpret the experimental results in terms of the principle of conservation of orbital symmetry. This resulted from the fascination that the order and predictions of the Woodward-Hoffmann rules exerted on practicing synthetic organic chemists. The assumption of concerted cycloreversion also seemed to be supported by unproductive attempts to demonstrate the existence of an intermediate **13** or **14** by trapping experiments, and by theoretical calculations which indicated an energy hypersurface without an intermediate[16]. In the meantime, however, convincing evidence has accumulated that [2+2]-cycloreversions generally occur in two steps.

The clarification of the question of a one- or two-step course for [2+2]-cycloreversions is not an end in itself, but constitutes a basis for preparative use of the reaction. On the basis of mechanistic studies to be presented, rules which govern the cycloreversion of four-membered ring compounds can be worked out.

2.1. Theoretical Calculations

The fragmentation of cyclobutane **15** into two molecules of ethylene **17** is to be seen as the prototype of [2+2]-cycloreversions. An earlier attempt to describe the energy hypersurface by a Hückel calculation argued against tetramethylene **16** as a true intermediate. Rather it was shown that the potential surface is characterized by a broad plateau. Here the molecule should remain long enough so that rotation around the single bonds should be possible and that this so called "twixtyl" form might also be trapped[16]. Consequently a twixtyl and a species in a potential well cannot, in principle, be differentiated.



15 **16** **17**

The unsatisfactory twixtyl model has not been confirmed by more exact calculations. *Segal*, using an *ab initio* method, found that a tetramethylene **16** is best assumed as an intermediate in the cleavage of cyclobutane[17]. A MINDO/3 calculation by *Dewar* led to the same result[18]. Reservations on the reliability of *ab initio*- and MINDO-approaches which were expressed in a critical review of the mechanism of the Diels-Alder reaction[19] are also valid for [2+2]-cycloreversions and therefore do not permit incontestable conclusions about this mechanism.

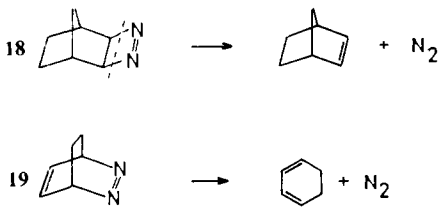
2.2. Kinetics

The thermal [2+2]-cycloreversion of many four-membered ring compounds in the gas phase or in solution exactly follows first-order kinetics. The fund of reliable acti-

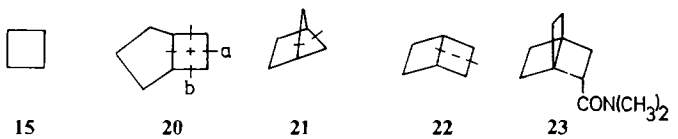
vation parameters[20–23] is notably rich, and will be discussed in its relevance to the reaction mechanism.

The activation energy for cleavage of cyclobutane **15** into two molecules of ethylene **17** is, at 62.5 kcal/mol[24], fairly large. This may be taken as an indication that the geometrically favorable $[\sigma 2_s + \sigma 2_s]$ path is contrary to the conservation of orbital symmetry, and that the "allowed" $[\sigma 2_s + \sigma 2_a]$ path, because of the necessary twisting, leads to an energy-rich transition state. On the other hand, *Seebach* has pointed out that the measured value is approximately the difference between the C—C dissociation energy of an *n*-alkane (82 kcal/mol for the central bond of butane[25]) and the strain energy of cyclobutane (27.4 kcal/mol[26])[5] so that in the rate-determining step apparently only *one* CC bond is broken to give the 1,4-diradical **16**. *Benson*[22,27] has come to the same conclusion from a thermochemical estimate in which the measured activation energy for cleavage **15** → **17** is larger than the calculated energy difference between **15** and the diradical **16**. This approach has been criticized because the interaction between the unpaired electrons in **16** was not taken into consideration[18].

How much the transition from an "allowed" to a "forbidden" cycloreversion, which must therefore occur *via* the diradical path, costs in terms of activation energy becomes clear on comparison of the two heterocycles **18** and **19**. The elimination of N_2 from **18** at −78 °C proceeds by a factor of 10^{22} slower than in the presumably concerted retro-Diels-Alder reaction of **19**[28]. This corresponds to a difference in activation energy of about 18 kcal/mol.



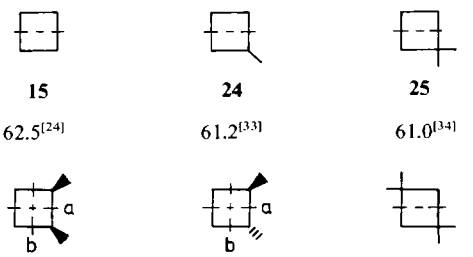
If the cyclobutane ring is part of a bi- or polycycle then the strain energy is increased and cleavage becomes easier. There is, in fact, a qualitative inverse correlation between strain energy and activation energy of [2+2]-cycloreversions (Scheme 1).



	15	**20**	**21**	**22**	**23**
E_{SE}[26] =	27.4	30.5	41.2	50.7	80–90
E_A =	62.5[24]	a: 64.0[29] b: 60.7	55.0[30]	36.0[31]	*ca.* 22[32]

Scheme 1. Relationship between strain energy E_{SE} [kcal/mol] and activation energy E_A [kcal/mol] of [2+2]-cycloreversions.

Alkyl substituents on cyclobutane should stabilize a diradical of type **13** relative to **16**, and thereby reduce the activation energy of [2+2]-cycloreversion. For increasing methyl substitution in **24**—**26** this appears to be confirmed (Scheme 2). The higher energy barrier in the tetramethyl derivative **27** is however unexpected. The same tendency is seen in the transition from cyclobutanone[38] to 2,2,4,4-tetramethylcyclobutanone[39].



	15	**24**	**25**
E_A =	62.5[24]	61.2[33]	61.0[34]
	cis-**26**	*trans*-**26**	**27**
E_A =	a: 60.4[36] b: 63.0	a: 61.7[36] b: 63.4	65.2[37]

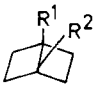
Scheme 2. Activation energies E_A (kcal/mol) of [2+2]-cycloreversions of methyl substituted cyclobutanes.

In bicyclo[2.2.0]hexanes **22** vicinal substitution actually retards cycloreversion[40].

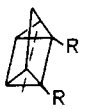
22b R = H; E_A = 34.5 kcal/mol
22c R = CH_3; E_A = 35.5 kcal/mol
22d R = C_2H_5; E_A = 36.2 kcal/mol
} in $Cl_2C{=}CCl_2$

As expected, functional groups which permit mesomeric stabilization of the radical intermediate **13** facilitate [2+2]-cycloreversion. Compared with the parent compound the energy barrier can be decreased by as much as 15 kcal/mol.

R =	$COOCH_3$	COC_2H_5	CHO	$CH{=}CH_2$
E_A =	57.3[41]	54.2[42]	53.3[43]	50.9 kcal/mol[44]

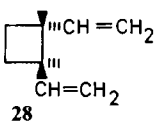


R^1 =	H	Cl	Cl	Cl	$COOCH_3$	CN
R^2 =	H	H	Cl	$COOCH_3$	$COOCH_3$	CN
E_A =	36.0[31]	34.5[40]	33.9[45]	30.2[46]	25.5[47]	21.7 kcal/mol[48]



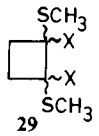
R = H; E_A = 38.3 kcal/mol[49] in toluene
R = $COOCH_3$; E_A = 34.9 kcal/mol in toluene

The possibility of both unpaired electrons in the diradical intermediate stabilizing themselves *via* allyl radicals makes **28** a particularly labile cyclobutane. The facile cycloreversion of compounds of type **29** which, at times, react even at room temperature[51] is apparently the result of capto-dative substitution which stabilizes the radical centers in a specific way[52].



28

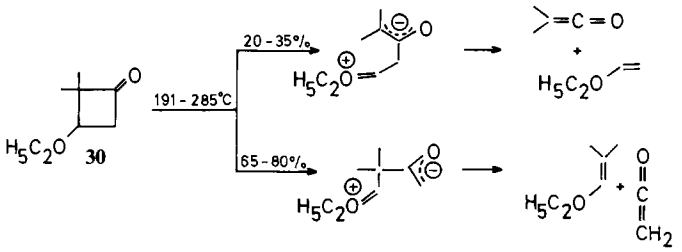
E_A = 32.2 kcal/mol[50]



29

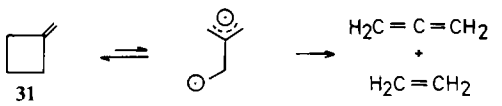
X = CN,CHO,$COOCH_3$, *etc.*

In four-membered rings with exocyclic double bonds the $[_\sigma 2_s + _\sigma 2_a]$-cycloreversion can be assisted by overlap of a σ orbital with the empty π^* orbital of the double bond[1]. In fact, the cycloreversion of cyclobutanone is more favorable by about 10 kcal/mol than that of cyclobutane **15**[38]. Alternatively, this effect is anticipated through the stabilization possibilities in the intermediate, which in the case of 3-alkoxy substitution as in **30** is particularly pronounced (E_A = 40.3 kcal/mol[53]).



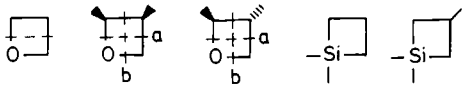
30

Methylenecyclobutane **31** represents a special case in which the intermediate recyclizes particularly easily so that the second step of the cycloreversion becomes rate-determining[54]. For complete ring cleavage, energies of 61.5 or 63.5 kcal/mol have been reported[55].



31

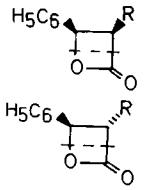
In oxetanes and siletanes (silacyclobutanes) exchange of a carbon atom in the cyclobutane by a heteroatom has only a slight influence on the energy barrier of the cycloreversion.



32 *cis*-**33** *trans*-**33** **34** **35**

E_A =	60.6[56]	a:62.5[57] b:63.2	a:63.7[57] b:64.7	62.3[35]	63.3 kcal/mol[58]

Comparison of **32** with **33**, and **34** with **35** demonstrates that these cycloreversions, as in the case of **27**, are retarded when more highly substituted. The same effect is encountered in 2-oxetanones[59].



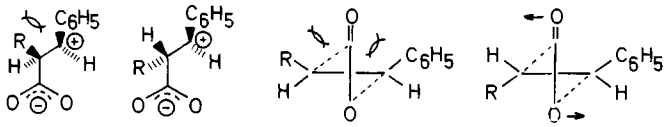
R =	CH_3	$CH(CH_3)_2$	$C(CH_3)_3$
k_{rel} =	1	0.31	0.028
k_{rel} =	11	4.3	2.1

A surprising difference appears in the influence of stereochemistry on the ease of bond breaking. In the 1,2-dimethylcyclobutanes **26** and the 2,3-dimethyloxetanes **33**, as well as the 2,3-dimethylcyclobutanones **60**[60] and tricyclo[4.2.0.$0^{2,5}$]octanes **99**[61] the *cis* compounds fragment faster in accord with their larger ground state steric interaction. With 2-oxetanones, however, the *trans* compound decarboxylates more easily. Three explanations for this and similar compounds have been considered:

1. Formation of the C=C bond during cycloreversion, starting from the *cis* compound results in stronger repulsion between the substituents. This effect was invoked by *Durst* to explain the fragmentation of stereoisomeric β-sultines[62,63] (cf. Section 3.5.1.), and could also explain the high thermal stability of highly fluorinated cyclobutanes[64].

2. In the dipole **36** resulting from a *cis*-oxetanone, the group R hinders the mesomeric stabilization of a positive charge by the phenyl group thus making **36** energy-rich relative to the *trans*-dipole **37**[65].

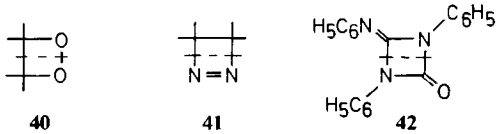
3. Assuming a concerted $[_\sigma 2_s + _\sigma 2_a]$-cycloreversion the substituents R or phenyl can avoid steric interactions with the oxygen atoms in a transition state analogous to **11** by slight deformation of the *trans*-orientation **39** whereas no such leeway is available in the *cis*-configuration **38**[59].



36 **37** **38** **39**

Based on what has been presented a clear distinction between these alternatives is not possible. It would be desirable to know the influences of methyl/phenyl substituents on the cycloreversion in cyclobutanes and oxetanes, as well as to test the behavior of 3,4-dialkyl-2-oxetanones of defined stereochemistry.

The lability of the oxygen-oxygen bond causes the [2+2]-cycloreversion of 1,2-dioxetanes such as **40** to occur much faster than for oxetanes **32**; the influence of alkyl substituents on the activation energy is poorly understood[66]. The facile elimination of nitrogen from **41** can be attributed to ring strain in the diazetine, while the relatively low activation energy in the decomposition of **42** may be explained by the charge stabilization of the zwitterion intermediate.



40 **41** **42**

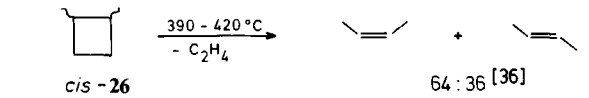
E_A =	27.6[66]	32.7[67]	28.2 kcal/mol[68]

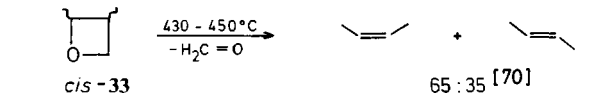
Besides the activation energies, the values of the *activation entropies* also support a two-step pathway for [2+2]-cycloreversion. In agreement with a conformationally flexible intermediate **13** or **14**, positive entropy values are usually observed, while for the concerted retro-Diels-Alder reaction the $\Delta S^{\neq}$ values lie near 0 cal $mol^{-1}K^{-1}$[19]. There have been reports of [2+2]-cycloreversions with negative activation entropies, which seem to be possible mainly in the fragmentation of polycyclic systems[69].

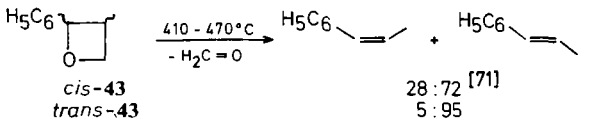
2.3. Stereochemistry

The most important consequence of the thermally allowed $[_\sigma 2_s + _\sigma 2_a]$ path of cycloreversion is inversion of configuration in the antarafacial component; in the photochemically induced four-membered ring cleavage the orientation of the substituents should remain unchanged according to the principle of conservation of orbital symmetry[1].

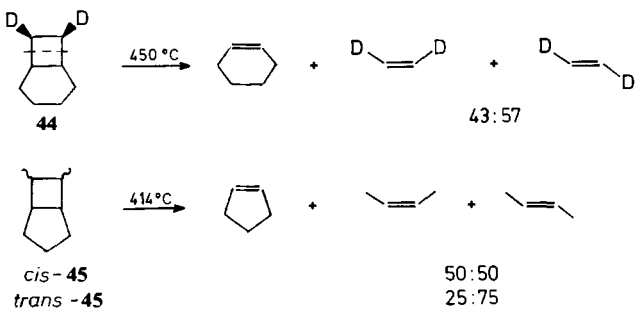
Experimentally, it has usually been found that partial retention of configuration occurs in the cycloreversion of 1,2-disubstituted four-membered rings. This tendency is more pronounced in *trans*- than *cis*-educts.



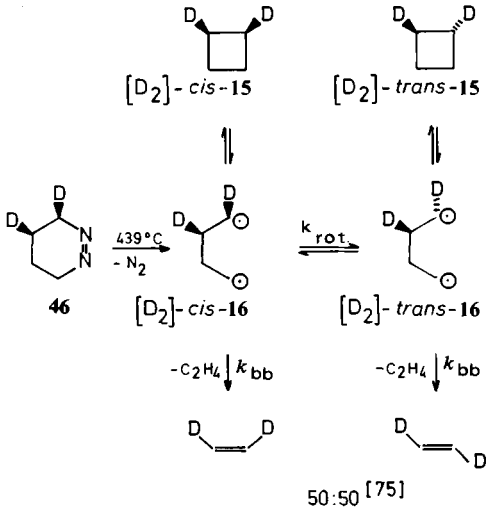




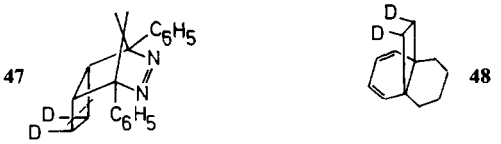
The lack of stereospecificity in **26**, **33**, and **43** does not in itself rule out a concerted cycloreversion since the *cis-trans* isomeric alkenes could represent either the supra- or the antarafacial fragment. Compelling evidence is seen in the cycloreversion of bicycles in which the four-membered ring is annelated onto a five- or six-membered ring. The resulting cycloalkene is now forced to be the suprafacial component while the other fragment—assuming a concerted reaction course—must by virtue of its antarafacial role suffer an inversion of configuration. The examples **44**[72] and **45**[73], however, show that this reorganization is only partially achieved.



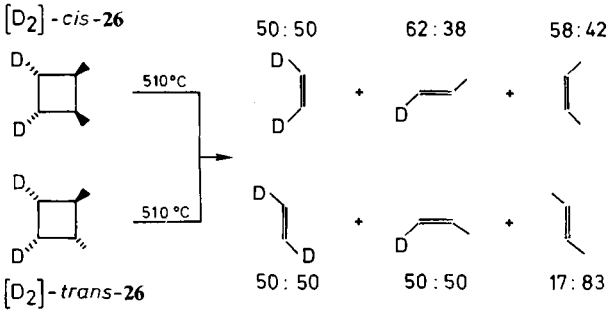
If the resulting *cis-trans* mixtures are described in terms of the diradical mechanism then the question of the relative rates of 2,3-bond breaking (k_{bb}) and rotation (k_{rot}) around the 1,2- and 3,4-bond in **13** arises. Numerous studies have shown that this ratio is strongly dependent upon the substituents, R^2 and R^4. Specifically, the ratio of k_{bb}/k_{rot} increases with the number of substituents, *i.e.* with changes from primary to secondary and finally tertiary groups, and the stereoselectivity also increases accordingly[74]. Thus, starting from $[D_2]$-*cis* and $[D_2]$-*trans*- **15**, diradicals **16**, in which rotation should be distinctly faster than cleavage, are formed. *Chickos* found essentially equal amounts of *cis*- and *trans*-1,2-dideuterioethylene[75] and a study of $[D_2]$-**16**, independently produced from tetrahydropyridazine **46** gave a value of 0.18 for k_{bb}/k_{rot}[76].



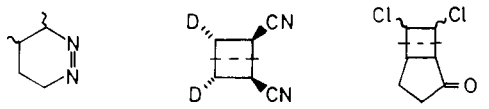
However, even with primary radical centers extensive or predominant retention is possible, as seen by formation of, respectively, 90 and 66% of *cis*-1,2-dideuterioethylene from the tricycles **47**[77] and **48**[78].



The dimethylcyclobutanes $[D_2]$-**26** permit complete stereochemical analysis of the cycloreversion products[79]. In the dideuterioethylene formed an equimolar mixture of *cis*- and *trans*-isomers is found, while for the 2-butene fraction, as in examples **26**, **33** and **43**, partial retention is observed. The k_{bb}/k_{rot} ratios were determined to be 1.24 from $[D_2]$-*cis*-**26** and 2.24 from $[D_2]$-*trans*-**26**, whereas the diradicals independently produced from **49** at 439 °C gave values of 1.13 and 3.0, respectively[80].

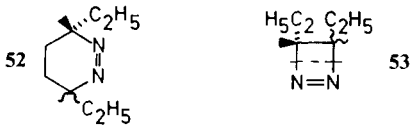


That rotation and cleavage occur at comparable rates with secondary radical centers is in agreement with the partial stereoretention observed in **50**[81] and **51**[82].



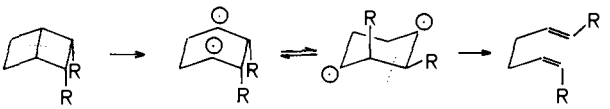
49 50 51

In triply substituted radical centers rotation is almost completely suppressed relative to cleavage. On the basis of fragmentation of heterocycle **52**, the ratio k_{bb}/k_{rot} in the diradical can be estimated to be *ca.* 50[83]. In agreement, the cycloreversion of the *cis-trans*-isomers of **53** occurs with >95% retention[84].



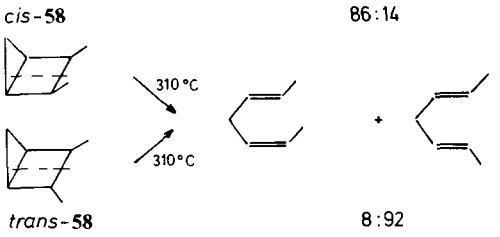
52 53

A special situation arises if the cyclobutane unit is annelated onto an additional small ring. In the thermolysis of bicyclo[2.2.0]hexanes **54** (R=D[85], CH_3[86], $COOCH_3$[87]) predominant inversion of configuration at one carbon atom occurs which otherwise was only observed for **44**. Although the stereochemistry corresponds to a $[\sigma 2_s + \sigma 2_a]$ process, a transition state of type **11** can hardly be considered because of geometric limitations. In order to explain formation of the (*Z, E*)-diene **57** a conrotatory ring opening of the diradical **55** was originally suggested[86]. After detailed experimental studies and theoretical calculations the observed stereochemistry was easily explained by conversion of the diradical from the boat- **55** into the chair-conformation **56**[61,88].

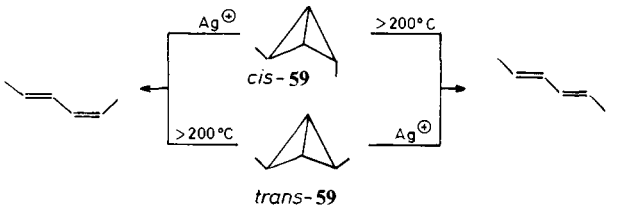


54 55 56 57

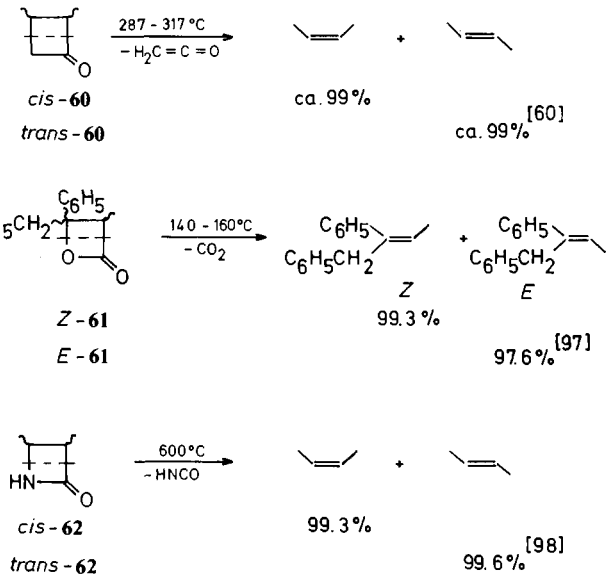
Similar to **54**, thermolysis of *cis*- and *trans*-bicyclopentanes **58** gives, respectively, 83 and 92% inversion of configuration, this has been explained by a conrotatory ring opening[89].



Several groups have studied the stereochemistry of ring-opening of bicyclo[1.1.0]butanes **59**. The central bond is not cleaved but [2+2]-cycloreversion with inversion of configuration at one carbon atom to give 1,3-dienes is observed[90,91–94]. Extensive retention is observed, however, if ring opening is catalyzed by metal ions (cf. Section 3.1.3)[95,96].

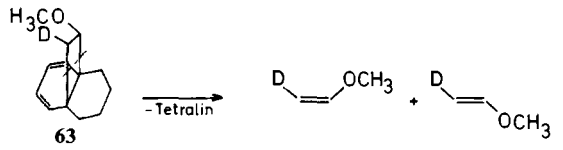


If a carbonyl group forms part of the four-membered ring then the transition state **11** of the $[\sigma 2_s + \sigma 2_a]$ reaction is somewhat more energetically favorable (cf. Section 2.2). In the examples studied a high degree of stereoselectivity is found; this has frequently been demonstrated for 2-oxetanones, in particular[99].



Since the product with the cumulative double bonds is in any case the antarafacial component, the stereoretention observed in the olefin fragment is in agreement with the Woodward-Hoffmann rules[1], and is greater than that with the simple 1,2-disubstituted cyclobutane examples discussed earlier. Alternatively, an intermediate, best formulated as a zwitterion, has been suggested in which interactions between the charged centers are possible, thus hindering rotation about the potential double bond[100]. The criterion "stereochemistry" therefore does not provide unequivocal evidence on the reaction mechanism. The mechanism involving zwitterions, however, fits the general picture better, and the involvement of charges also explains the observed regioselectivity of the cycloreversion (cf. Section 2.4).

For *photochemical* [2+2]-cycloreversions of four-membered rings a higher degree of stereoretention is to be expected because of the "allowed" geometrically favorable transition state **12**. The ratios, however, closely resemble those reported for the thermal process. Here too, the four-membered ring fragmentation usually follows a two-step pathway. If the intermediate diradical is produced with high excess energy, then the "stereochemical leak" can be even greater than in the thermal cycloreversion; this is demonstrated by comparison of the thermal and photochemical fragmentation of **63**.

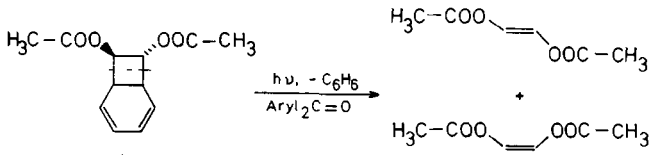


63

314 °C[78]
hν[101]

97:3
88:12

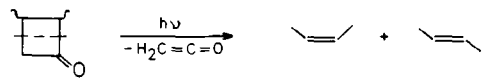
In some cases, the photochemical [2+2]-cycloreversion can be strongly influenced by the photolysis conditions. An extreme example is **64**, which undergoes electrocyclic ring opening upon direct irradiation[102], but which fragments with the expected partial stereoretention when photolysis is performed in the presence of aromatic ketones[103].



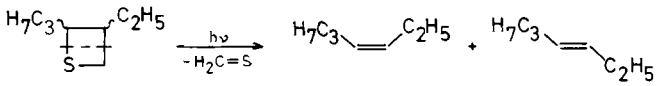
64

60 : 40

The medium and wavelength also influence the stereochemical course of the photochemical cycloreversion, as studies with **60** and **65** show.



cis-**60**	>94 : <6	(gas phase)[104]
	80 : 20	(benzene)[105]
	94 : 6	[$(CH_3)_3COH$][106]
trans-**60**	<6 : >94	(gas phase)[104]
	3 : 97	(benzene)[105]
	1 : 99	[$(CH_3)_3COH$][106]



cis-**65**	43:57 (254 nm, Hg)[107]
	34:66 (313 nm)
trans-**65**	22:78 (254 nm, Hg)
	13:87 (313 nm)

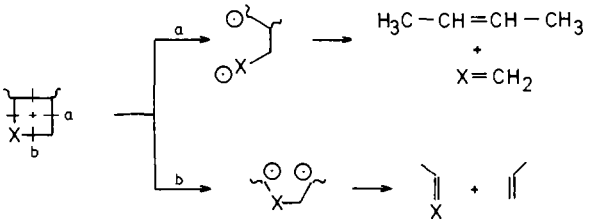
2.4. Regioselectivity

Which pair of σ-bonds of a four-membered ring is broken during cycloreversion is a decisive factor for the preparative use of this reaction type. Two effects, at times opposing, are seen from mechanistic studies:

1) The relative strength of the four-membered ring bonds in the ground state.

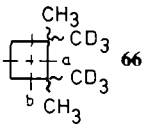
2) The stability of the diradical or zwitterionic intermediate which can be influenced through substituents or solvent.

In 1,2-disubstituted four-membered rings, the 1,2-bond has the lowest bond order[108] and is ruptured to a relatively stable - on both radical centers secondary - diradical. The preference for cleavage route "a" is most notable with *cis*-**26**. That the interaction of the substituents in the ground state is decisive is demonstrated by the cycloreversion of **33** and **60**: the ratio a/b is not reversed, although cleavage "b" leads to formation of a radical center α to an O atom or carbonyl group that is energetically favored.



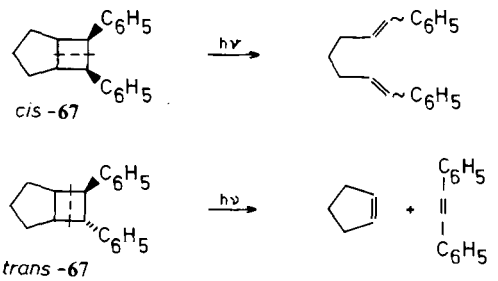
	cis-**26**	*trans*-**26**	*cis*-**33**	*trans*-**33**	*cis*-**60**	*trans*-**60**
X=	CH_2	CH_2	O	O	CO	CO
a/b=	6.8[80]	3.3[80]	2.1[70]	1.2[70]	5.8[96]	1.1[96]

Furthermore, in stereoisomers of **66** in which the 1,2-bond is completely substituted only cleavage by path "a" is observed[109].



66

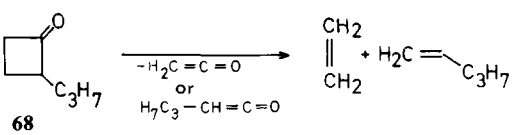
For light-induced [2+2]-cycloreversion of cyclobutanes, numerous examples illustrate that the relief of steric interaction in the ground state determines the regioselectivity of the cleavage. The reaction pathway favored here is also followed even if it leads to a less stabilized diradical[110]. This "*cis*-effect" becomes clear in the different behavior of the *cis*- and *trans*-isomers of the bicycle **67** under direct light-excitation[111].



cis-**67**

trans-**67**

In the photochemistry of cyclobutanones, decarbonylation to give cyclopropanes, and ring expansion to give tetrahydrofuran derivatives compete with the [2+2]-cycloreversion[105, 112, 113]. The regioselectivity of the photochemical cleavage of the four-membered ring can be less marked than in thermolysis shown in example **68**[114].

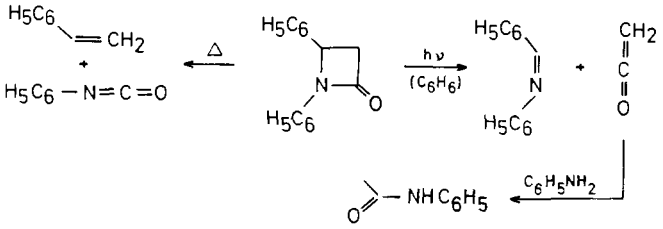


68

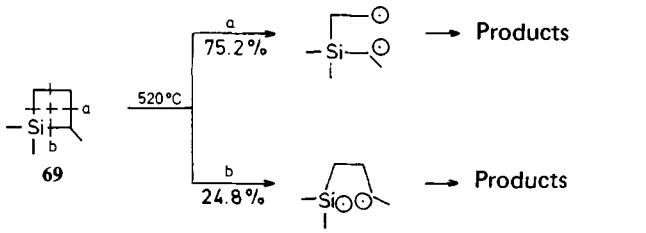
350 °C
hν, 325 nm

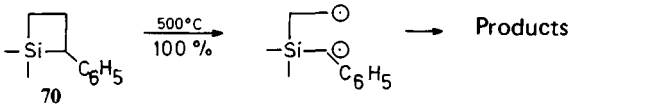
78 : 22
56 : 44

In the photolysis[115] of 2-azetidinones the regiospecificity observed in the thermal[116] cycloreversion is often completely reversed. For both cleavage directions the reaction probably occurs from the excited singlet state[115].

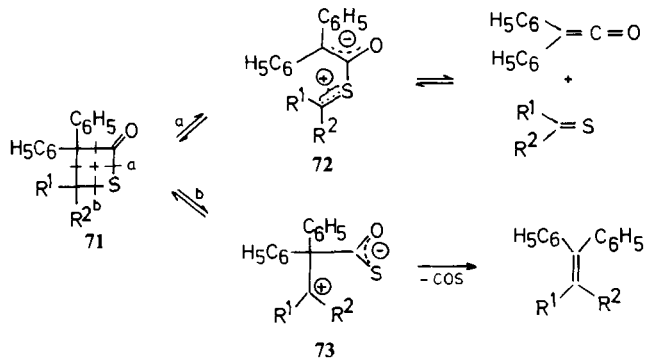


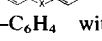
Examples in which the stability of the diradical intermediate determines the regioselectivity of the cycloreversion are found in the chemistry of siletanes. The stabilizing effect of silicon on an unpaired electron in the β-position, despite the "*cis*-effect", facilitates cleavage corresponding to "a" starting from **69**[117]. In **70**, exclusively products resulting from 2,3-bond breaking can be detected[118].





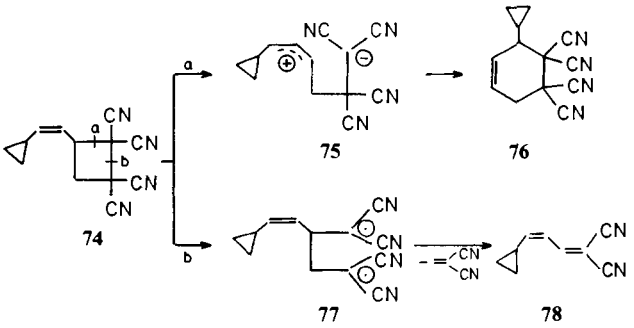
Also, if a possible zwitterionic intermediate is specifically stabilized, this effect can determine the regioselectivity of the cycloreversion. This is indicated by the decomposition of **30**, as well as of **71**. The 2-thietanones **71** resulting from the reaction of diphenylketene and thiobenzophenones generally undergo cycloreversion upon warming to give the educts[119,120]; however, if *both* phenyl residues of the thioketone are substituted by amino groups in the *p*-position, elimination of carbonyl sulfide occurs to give the alkene[119,121]. Apparently the particularly electron-rich groups R^1,R^2 stabilize the positive charge so well that reaction path "b"—irreversible in the last step—can compete with path "a".



Path a: $R^1=R^2=C_6H_5$; $R^1=R^2=4\text{-}CH_3OC_6H_4$;
$R^1+R^2=$  X=O, S;
$R^1=4\text{-X—}C_6H_4$ with X=$(CH_3)_2N$, Cl, $(CH_3)_2CH$,
$R^2=C_6H_5$

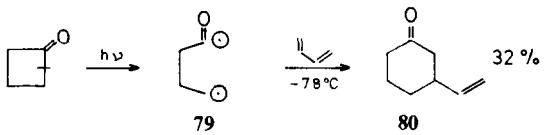
Path b: $R^1=R^2=R^3{}_2N\text{—}C_6H_4$ with $R^3=CH_3$, C_2H_5
$R^1+R^2=$

The solvent effect on the regioselectivity of [2+2]-cycloreversions has only been studied in a few examples. In the decomposition of oxetanes, the effect is slight[122]. The alkenylcyclobutane **74** on the other hand shows a marked dependence of the regioselectivity on the solvent[123]. Bond breaking according to path "a" leads here to an intermediate best formulated as a zwitterion; therefore, in polar solvents this path is taken and a cyclohexene **76** is isolated *via* ring expansion. On the other hand, in the non-polar cyclohexane besides 26% **76**, 67% of the diene **78** is formed *via* the diradical **77**[123].

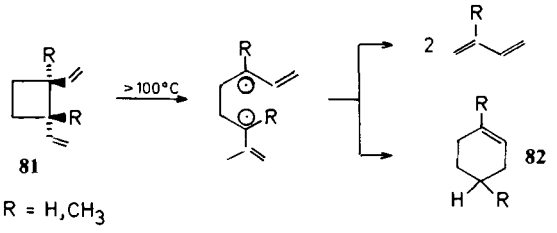


2.5. Trapping and Isolation of the Intermediate

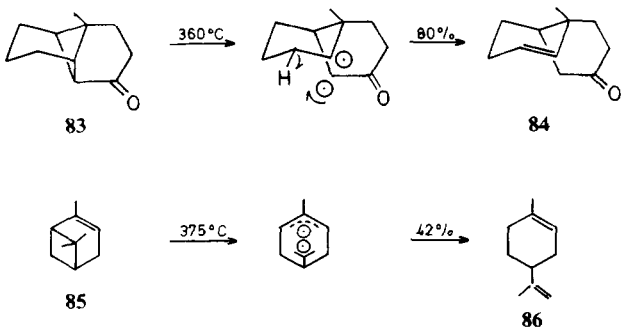
There has been no lack of experiments to trap the presumed 1,4-diradicals in [2+2]-cycloreversions since such reactions deserve study from preparative as well as mechanistic interests. For *inter*molecular trapping reactions, however, there are only a few examples. During photolysis of cyclobutanone in 1,3-butadiene, *Dowd, Gold,* and *Sachdev*[124] found an adduct **80** derived from both components that apparently resulted from reaction of the diene with the diradical **79**. Thus **79** is *mutatis mutandis* to be viewed as the intermediate in the [2+2]-cycloreversion of cyclobutanone.



In view of the usually very short lifetime of the intermediate **13** or **14** the subsequent *intra*molecular reactions are more likely than reaction with trapping reagents. One example, the ring expansion of **75** to **76**, has already been presented. Similarly, a cyclohexene **82** is formed in the thermolysis of *trans*-1,2-divinylcyclobutanes **81**[50,125].

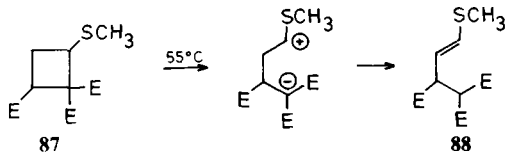


A further possibility for intramolecular stabilization of 1,4-diradicals is hydrogen abstraction. The disproportionation of the diradicals obtained from the tricycle **83**[126] as well as from α-pinene[127] can be mentioned as examples.



83 84 85 86

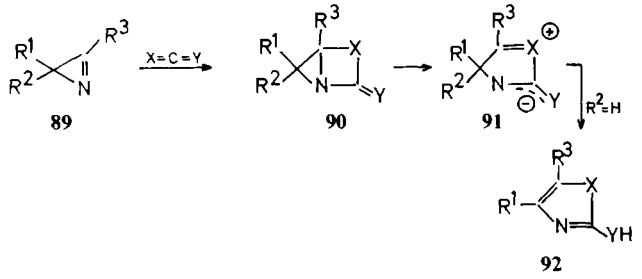
In the 1,4-zwitterions **14** with $R^1 = H$ a 1,3-hydrogen shift occurs particularly easily to the anion moiety. Thus, the cyclobutane **87** is converted into the vinyl sulfide **88** by slight warming[128].



87 88

E = $COOCH_3$

2-Monosubstituted azirines **89a** and **89b** react with cumulative double bonds to give highly strained cycloadducts **90**, which undergo *in situ* four-membered ring opening to produce the zwitterions **91**. Stabilization follows by hydrogen shift to the anionic center. As educts, besides isocyanates[129] carbon disulfide, isothiocyanates[130,131] and thioketenes[132] have been used.

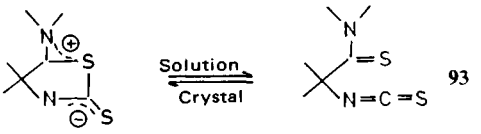


89 90 91 92

89a, $R^1 = CH_3$, $R^2 = H$, $R^3 = C_6H_5$
89b, $R^1 = CON(CH_3)_2$, $R^2 = H$, $R^3 = N(CH_3)_2$
89c, $R^1 = R^2 = CH_3$, $R^3 = N(CH_3)_2$
89d, $R^1 = R^2 = CH_3$, $R^3 = N(C_2H_5)_2$
89e, $R^1 = R^2 = CH_3$, R^3 = morpholino
90—92, X = O, S; Y = S, NAryl, $NCOC_6H_5$, $C(Alkyl)_2$

In 1,4-zwitterions the charge stabilization can be so extensive that they can be isolated[133]. Reaction of the 3-dialkylaminoazirines **89c—e** with benzoyl isothiocyanate[134], carbon disulfide[135—137], carbon diselenide[138], or thioketenes with electron withdrawing substituents[132] yields crystalline, slightly soluble 1 : 1 adducts, which on the basis of spectroscopic data, chemical properties, and X-ray crystallographic analyses[134,135] have the zwitterionic structures **91**. Of particular note is the behavior of the adduct obtained from carbon disulfide: in solution the bifunctional cycloreversion product **93** is detectable, while in the crystal form only the zwitterion is present. The reaction is completely reversible[135].

The corresponding selenium compound behaves in a similar fashion[138].



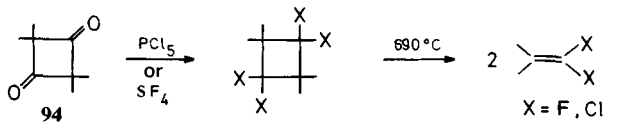
93

3. Applications

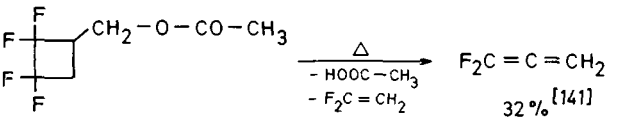
3.1. Cyclobutanes

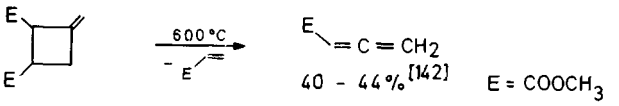
3.1.1. Thermal [2+2]-Cycloreversions of Cyclobutanes

Cleavage of simple cyclobutanes often only leads to trivial products. Exceptions are the preparation of 1,1-dihalo-2-methylpropenes from the easily available cyclobutanedione **94**[139], and of functionally substituted allenes[140—142].

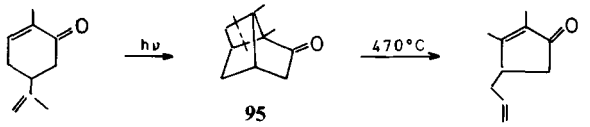


94



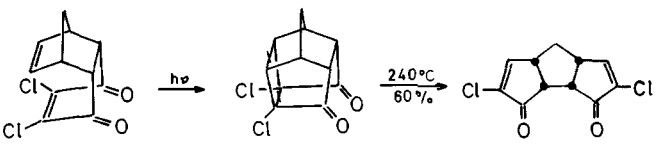


Interesting systems are derived from cycloreversion of four-membered rings that are part of bi- or polycyclic systems. In the simplest case the ring cleavage serves as a structural proof—as with **95**, which resulted from irradiation of carvone with sunlight[143].



95

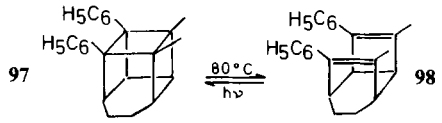
One strategy for preparation of polycyclic cyclopentanoids starts from cage compounds such as **96**[144].



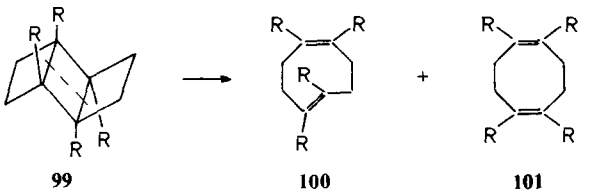
96

Whereas in the case of **96** the thermal cycloreversion proceeds contrary to the photochemical mode of formation, in other cases thermolysis regenerates the starting material. Thus, the cage compound stores light energy and liberates it later as thermal energy. In the case of the polycycle **97**, regeneration of the diene **98** occurs with a Q-

value of 12% at 290 nm[146], characterising the capacity of the energy-storage[145].

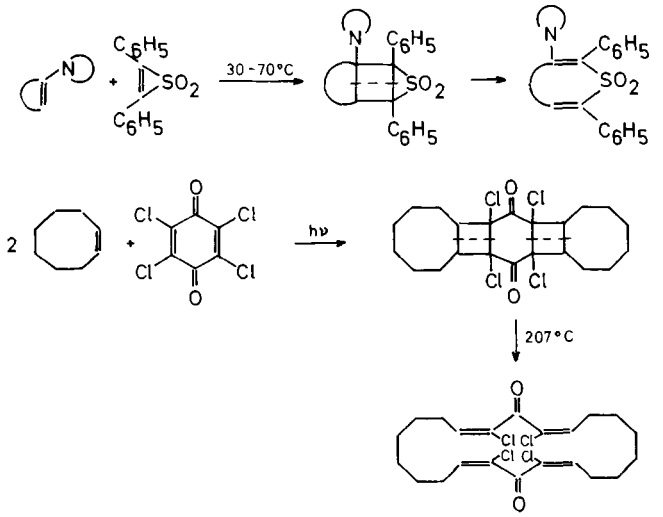


The cycloreversion of the tricycles **99** takes place in the highly strained central ring to give 1,5-cyclooctadienes **100** and **101**. Here, a **56**-analogous diradical intermediate is assumed[61] so that the *cis-trans*-diene **100** predominates and the reaction can be used preparatively for this stereoisomer[48, 147].



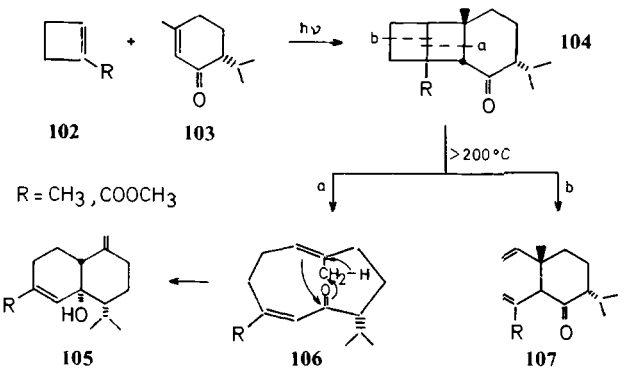
R = CN, $COOCH_3$

Medium S-rings with 9 to 15 members are available thermally from the cycloaddition of 1-aminocycloalkenes with thiirene *S,S*-dioxides and subsequent [2+2]-cycloreversion[148]. With two equivalents of cyclooctene and chloranil the cycloreversion leads to a C_{22} macrocycle[149].



Several groups have used the cycloreversion of tricyclo[4.4.0.$0^{2,5}$]decanes **104** to synthesize sesquiterpenes[150–153]. Here a terpene ketone **103** is first added photochemically to a cyclobutene **102** as an isoprene building block. The cycloreversion then cleaves the central or outer four-membered ring to give **105** or **107**, respectively. With **105** a subsequent facile intramolecular ene-reaction leads to the *trans*-decalins **106**[151b,c]; by changing the thermolysis conditions[150, 153b] or after reduction of the carbonyl group[150b, 151a, 152] the reaction stops at the intermediate stage **105**. **105**—**107** are sesquiterpenes having the germacrane, cadinane, and elenene skeletons, respectively.

The [2+2]-cycloreversion can also serve to modify, as well as to synthesize terpenes. Pyrolysis of compounds

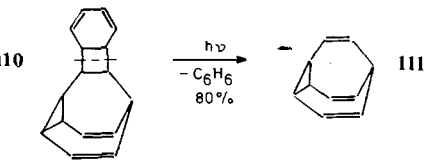


R = CH_3, $COOCH_3$

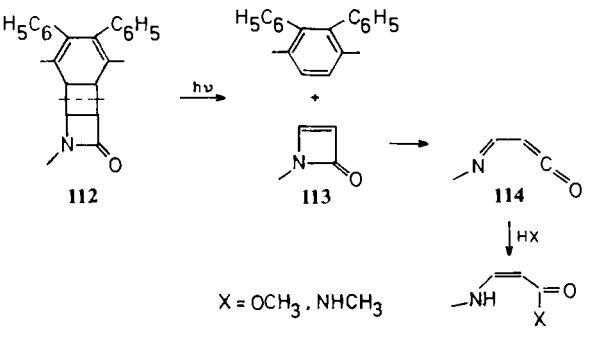
having the pinane skeleton leads to cleavage of the four-membered ring to give 1,6-dienes, which either themselves or subsequent reaction products such as **86** are important in the perfume industry[154]. As a simple example, the cycloreversion of (−)-*cis*-pinane **108** to the diene **109** is given[155]. Pyrolysis of derivatives with hydroxy[156] or carbonyl functions[157] or of pinene **85**[127] also yields useful products.

3.1.2. Photochemical [2+2]-Cycloreversions of Cyclobutanes

Cyclobutanes which are attached to an arene, polyene, or carbonyl group as a chromophore can be easily split photochemically into two olefinic fragments. Photochemical [2+2]-cycloreversions in which one of the fragments can form an aromatic system are especially favored and regioselective. An already classical example of this can be seen in the bullvalene synthesis of *Schröder*[158].



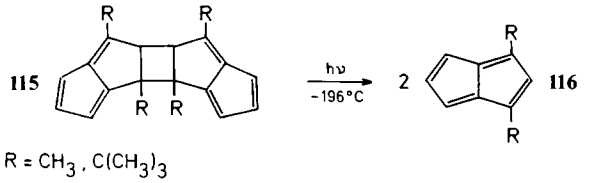
With tricycle **112** cycloreversion of the central ring liberates the azetinone **113**. Under the reaction conditions this unusual heterocycle undergoes electrocyclic ring opening to give ketene **114**, which is finally trapped by added nucleophiles such as methanol or methylamine[159].



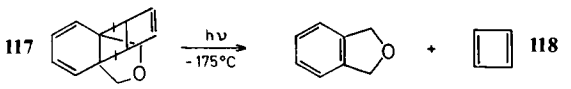
X = OCH_3, $NHCH_3$

Using the matrix technique, high-energy compounds from photochemical [2+2]-cycloreversions can be ob-

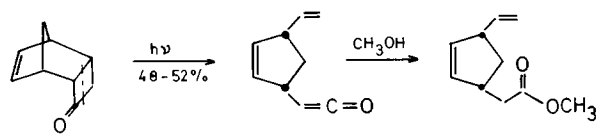
tained and characterized at low temperatures. This holds for preparation of the pentalenes **116** from their dimers **115**[160], as well as for the liberation of cyclobutadiene **118** from various precursors[161] such as the propellane **117**[162].



R = CH_3, $C(CH_3)_3$

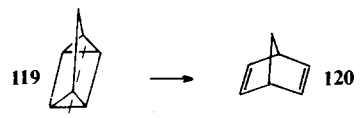


The photochemical [2+2]-cycloreversion of cyclobutanones has been studied primarily from the mechanistic point of view[112, 113]. The reaction finds synthetic application in the preparation of functionalized cyclopentene derivatives[163].



3.1.3. Catalytic [2+2]-Cycloreversions of Cyclobutanes

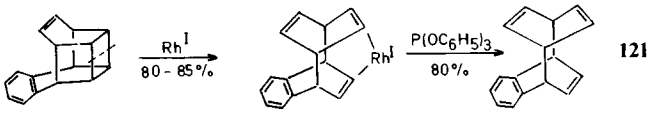
Towards the end of the sixties *Hogeveen et al.* proved that the activation energies for [2+2]-cycloreversion of hexamethylprismane[164] and quadricyclane[165] (Scheme 3) are drastically lowered by rhodium, palladium, or platinum coordination compounds. Subsequently, this aspect of cycloreversions has been intensively studied[166]. In general, metal catalysis is only effective in cases of pronounced ring strain, so that cleavage of cyclobutane proceeds only to a minor extent[167]. On the contrary, catalysis by metal salts or coordination compounds has been used successfully for derivatives of **119**, as well as for bicyclo[1.1.0]butanes like **59**[95, 166a,b,d], for *syn*-tricyclo-[4.2.0.$0^{2,5}$]octanes[166a, 168], and for cage compounds such as cubane[169]. Recent synthetic applications are the indirect synthesis of the *p,p'*-cycloadduct **121** from benzene and naphthalene[170], and the ring expansion of cycloalkenes to 1,3-cycloalkenes, *e.g.* **122**→**126**[166d]. *Paquette et al.* elegantly applied this method in a six-step synthesis of heptalene **127** from naphthalene[171].

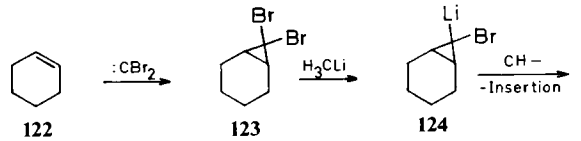


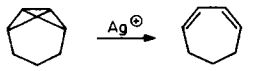
140 °C, without catalyst: $t_{1/2} > 14$ h
−26 °C $[Rh(BCH)Cl]_2$: $t_{1/2} = 45$ min

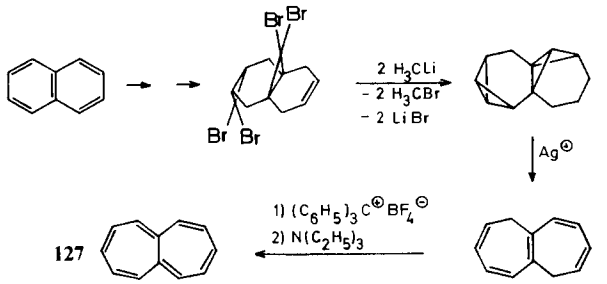
Scheme 3. Half-lives $t_{1/2}$ of the transformation **119**→**120** under different conditions (BCH = bicyclo[2.2.1]hepta-2,5-diene) [165].

In combination with the photochemical formation of four-membered rings the metal catalyzed cycloreversion has been discussed as a method for solar energy storage.

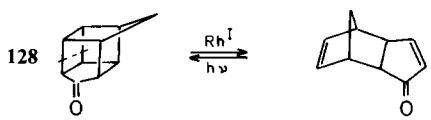




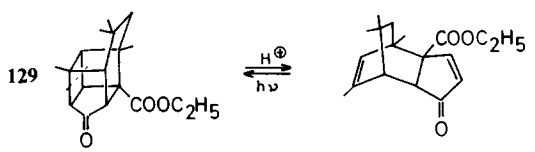




Besides the system **119** ⇌ **120**[172], particularly cage compounds like **128**[173] are being studied for this purpose. So far practical applications remain elusive because of the insufficient stability in multiple reaction cycles.

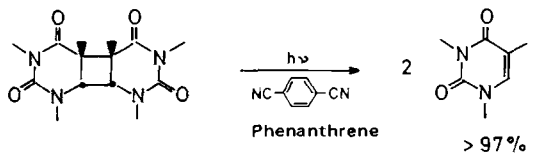


In addition to the use of metal complexes, the energy stored in cage compounds can also be liberated by acids[174]. In the case of the pentacycloundecanone **129** [2+2]-cycloreversion is strongly exothermic by 21.7 kcal/mol, rendering the system particularly interesting from the point of view of energy storage[175].



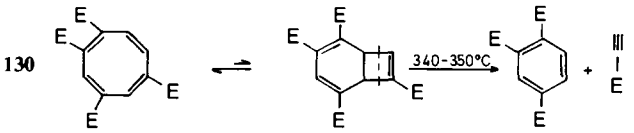
[2+2]-Cycloreversions can also be induced by electron transfer to an acceptor molecule. Formation of the radical cation can take place in the dark by irradiation of the charge transfer complex between four-membered ring compounds and acceptors, or *via* interaction with an electronically excited acceptor[176]. An example for the first-mentioned possibility is found in the cleavage of the *cis-syn* dimer of dimethylthymine which is induced by the phenanthrene radical cation generated in a sensitized pho-

toreaction. The reaction is of interest as a model for the enzymatic photoreactivation of damaged DNA[177].

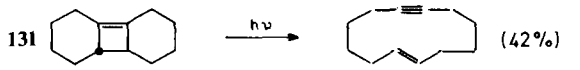


3.2. Cyclobutenes

Cyclobutenes react thermally under electrocyclic ring opening to give butadienes. An exception, the pyrolysis of cyclooctatetraene **130** carried out as a structural proof, can be mentioned[178].



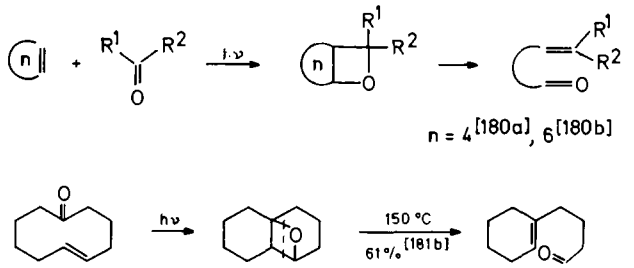
In the photochemistry of cyclobutenes, butadiene formation is less dominant than cycloreversion to an alkyne and an alkene[110a]. This decomposition pathway can even be detected in the parent compound[179a], and is particularly favored if the allowed disrotatory electrocyclic ring-opening would lead to *trans*-cyclohexene, as in tricycle **131**[179b].



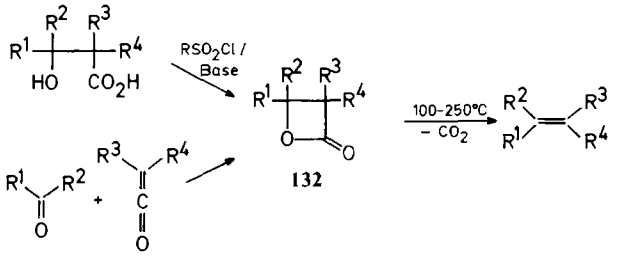
3.3. Four-Membered Rings with One Heteroatom

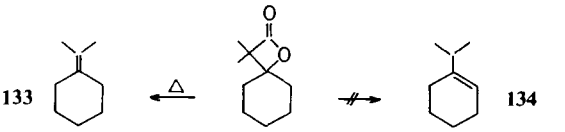
3.3.1. Oxetanes

The cycloreversion of oxetanes is synthetically important if the heterocycle is annelated to a second ring. Such bicycles are easily accessible *via* Paterno-Büchi reaction of cycloalkenes with aldehydes or ketones, and on cycloreversion yield carbonyl compounds with a remote double bond[180]. Intramolecular modifications of the reactions have also been reported[181]. Yields are higher with proton or metal catalysis than in the simple thermolysis[180b].

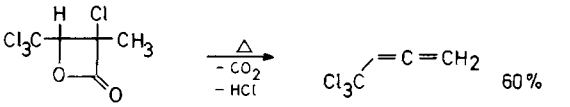


The cycloreversion of 2-oxetanones **132** introduced by *Staudinger* has found broad application[182]. Starting from a 3-hydroxycarboxylic acid or by cycloaddition of a ketene with a carbonyl compound, heterocycles **132** are readily accessible. Because of the stereospecificity of the fragmentation (cf. Section 2.3.) and the smooth formation even of tri- and tetrasubstituted alkenes, the method ably compliments the classical Wittig olefination. Another advantage is that the olefination proceeds without hydrogen shifts, hence **133** can be obtained free of isomers; using a Wittig reaction **134** was also obtained[97].

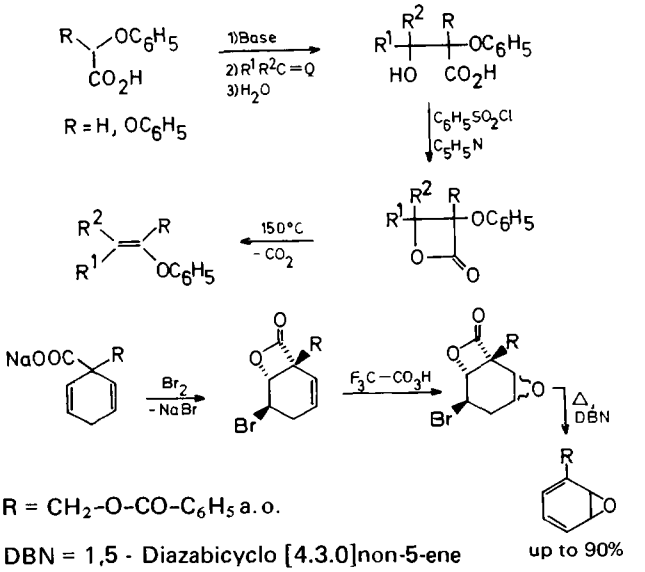




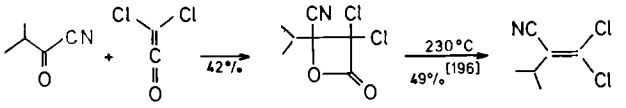
In contrast, decarboxylation of **132** is hindered if R^3 is a silyl residue[183] or by halogen substitution, particularly for $R^1 = CCl_3$[185]; in a ketene generator, however, fragmentation is accomplished in such a case, and leads, with concomitant elimination of hydrogen chloride, to an allene.



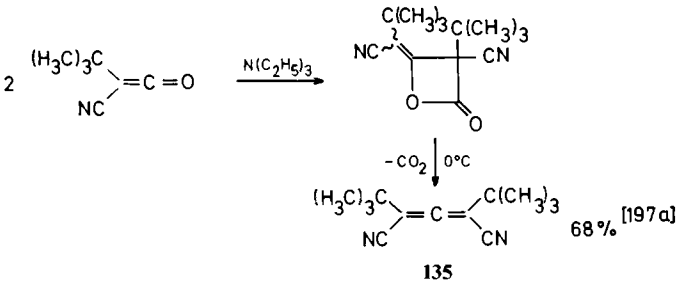
On the other hand, carbon dioxide is eliminated particularly readily if R^1 can stabilize a positive charge at the 4-position of **132**, *i.e.* in 2-oxetanones which result form ketene addition to benzaldehydes[186], cyclopropenones[187], tropones[187b, 188], phenalenone[187b, 189], thiapseudophenalenones[187b, 190], or compounds of the γ-pyrone type[191]. Quinones have also been successfully employed as precursors[192]. Special applications are found in the preparation of aryl enol ethers and ketene diphenyl acetals, which are otherwise obtained only with difficulty[193], and of arene oxides[194].



Attention has been directed to the highly reactive dichloroketene as a particularly interesting ketene component which allows dichloromethylenation of carbonyl compounds even where the Wittig reaction fails[185, 195, 196].

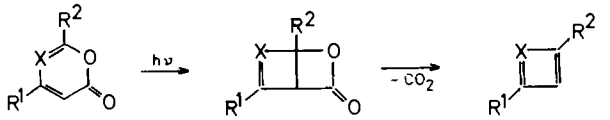


3-Alkylidene-2-oxetanones result from dimerization of ketenes[182a]; their decarboxylation makes symmetric allenes accessible[197], *e.g.* **135** which is strongly electrophilic due to the electron withdrawing nitrile groups[198].



135

On irradiation α-pyrone yields 2-oxabicyclo[2.2.0]hex-5-en-3-one. Its decarboxylation leads to cyclobutadiene **118** which was detected in a matrix at 8 K[199]. Possible formation of azacyclobutadienes **136** using this route has also been invoked[200].



X = CH, $R^1 = R^2 = H$ **118**

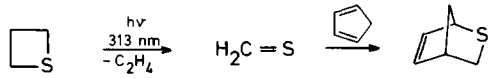
X = N, $R^1 = R^2 = H$ **136a**

X = N, $R^1 = CH_3$, $R^2 = C(CH_3)_3$ **136b**

A special use of the 2-oxetanones lies in the protection of one olefinic double bond in a polyene. This has been used in the synthesis of juvenile hormone analogs[201].

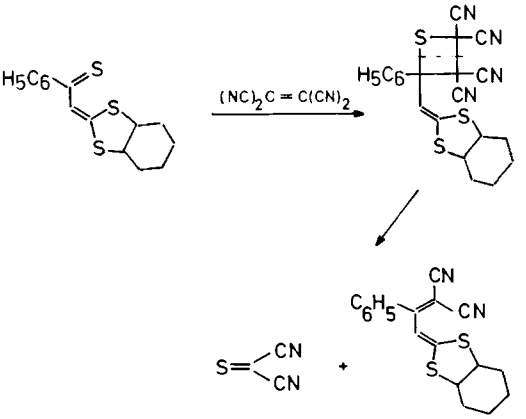
3.3.2. Thietanes

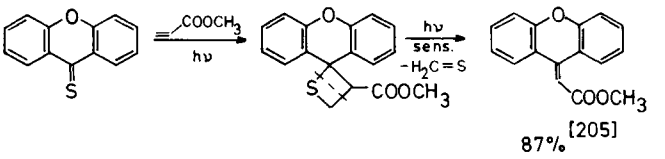
The [2+2]-cycloreversion of thietanes can be thermally or photochemically induced. Thus thioformaldehyde is formed by heating the parent system to 1000 °C[202] or by irradiation[203], and can be detected spectroscopically or trapped by Diels-Alder reaction with cyclopentadiene[203].



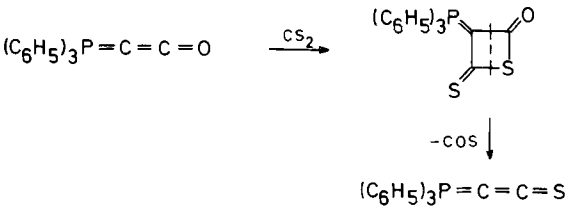
Because the cycloaddition of thiocarbonyl compounds, in contrast to the Paterno-Büchi reaction, often proceeds thermally and with electron-poor alkenes, fragmentation of these thietanes markedly expands the range of olefins available *via* oxetanes (cf. Section 3.3.1.)[204, 205].

Olefinations by reaction of thiocarbonyl compounds with ketenes followed by cycloreversion of the resulting 2-



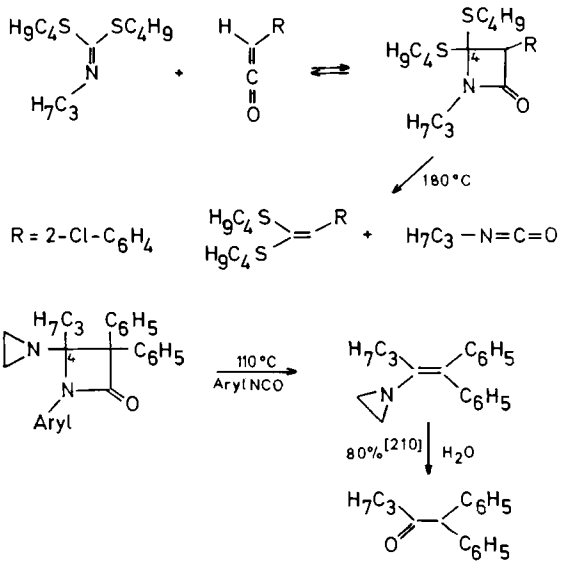


thietanones are possible, but are of synthetic interest only if the carbonyl compounds which serve as the precursors to the thiones do not themselves react with ketenes[119–121]. On the other hand, cycloreversion of 2-thietanethiones opens a route to those thiocarbonyl compounds, especially thioketenes, which are not available by direct sulfurization[206].

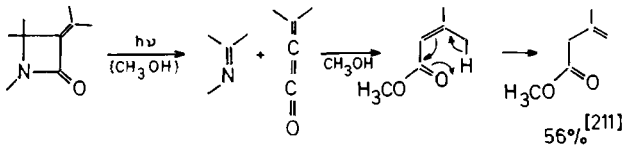


3.3.3. Azetidines

Cycloreversion of unsubstituted azetidine starts only at 400 °C[207], and simple 2-azetidinones ("β-lactams") are thermostable up to 500 °C[98]. As expected, the cycloreversion is significantly accelerated by electron donors in the 4-position[208–210].

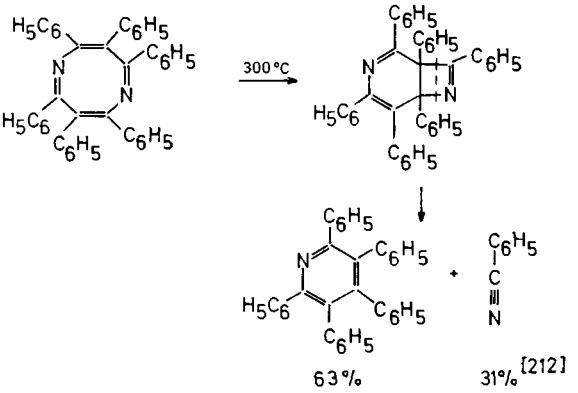


Generally, photochemical cleavage of 2-azetidinones gives fewer side products[115], however, the other cleavage direction occurs (cf. Section 2.4.). Starting from a 3-isopropylidene-2-azetidinone, an alkylideneketene is generated and trapped with methanol[211].



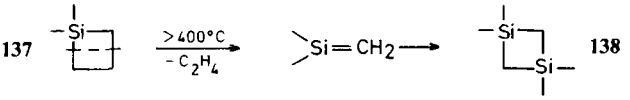
Cycloreversion of the β-lactam moiety of penicillin- and cephalosporin-derivatives catalyzed by trifluoroacetic acid gives a ketene and a thioimidic acid ester fragment[208].

1-Azetines fragment photolytically (cf. **136a, b**) or thermally[212], to afford hydrocyanic acid or a nitrile; electrocyclic ring opening is not observed.

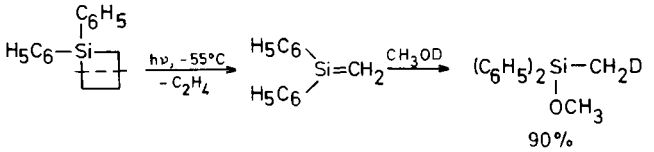


3.3.4. Siletanes

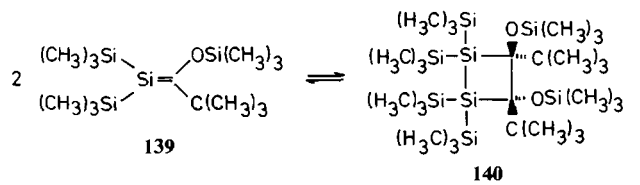
Because of their unique bonding properties, silaalkenes (silenes) are of particular interest. Although assumed for some time not to exist, a species of this type has been obtained through cycloreversion of siletane **137**[35,213].



With phenyl substitution the cycloreversion can also be accomplished by irradiation[214].

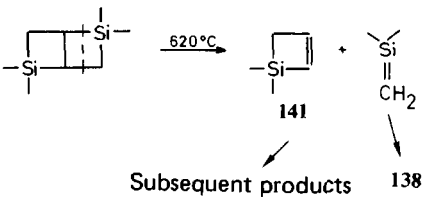


The silaalkene **139** is sufficiently stable that it occurs in solution together with the head-to-head dimer **140**[215].



139 **140**

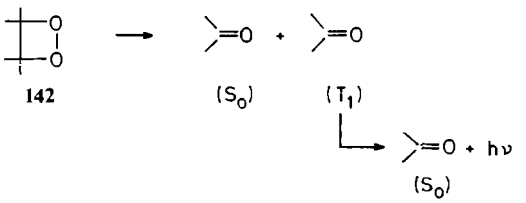
Barton et al. even succeeded in generating a siletene **141** *via* a [2+2]-cycloreversion[216].



3.4. Heterocycles with Two Identical Heteroatoms

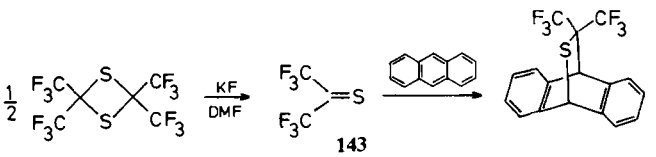
3.4.1. 1,2-Dioxetanes

If a concerted photochemical [2+2]-cycloaddition must follow the $[_\pi 2_s + _\pi 2_s]$ path[1], then a naive expectation for the $[_\sigma 2_s + _\sigma 2_s]$-cycloreversion would be chemiluminescence[217]. In fact, the cleavage of 1,2-dioxetanes such as **142** occurs with chemiluminescence. However, contrary to the expectations of the Woodward-Hoffmann rules, the light is emitted from the triplet acetone[218]. Because of the special interest in chemiluminescent systems, the cycloreversion of 1,2-dioxetanes and 1,2-dioxetan-3-ones has been intensively investigated[219]. At the forefront are mechanistic studies; of particular importance are the roles of 1,2-dioxetan-3-ones in bioluminescence[220] and the "photochemistry without light" studies mainly of *White et al.*, in which photoreactions are induced by heating photolabile substances with **142**[221].

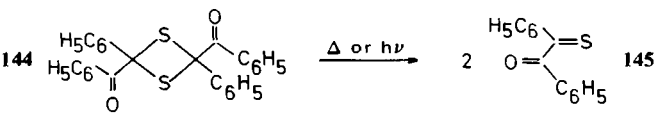


3.4.2. 1,3-Dithietanes

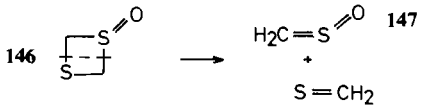
Thiocarbonyl compounds often tend to dimerize to 1,3-dithietanes. This can be an undesired side reaction, but the air-stable, storable 1,3-dithietanes present the possibility of liberating highly reactive C=S compounds by a [2+2]-cycloreversion. Hexafluorothioacetone **143**, prepared from hexafluoropropene and sulfur, dimerizes but can be regenerated in potassium fluoride/dimethylformamide (DMF)[222] or thermally[223], and allowed to react with anthracene in a Diels-Alder reaction.



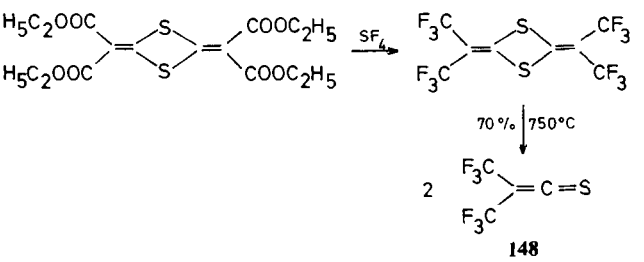
Bak and *Praefcke* reported that the dimer **144** can be converted thermally above 210°C into the monomeric monothiobenzil **145**, but by irradiation even at room temperature[224].



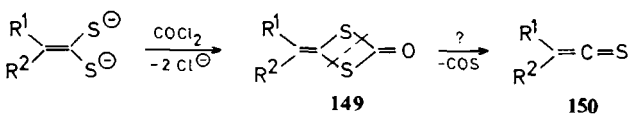
1,3-Dithietane 1-oxide **146** is a source of thioformaldehyde *S*-oxide ("sulfine") **147**, which can thereby be studied by microwave[225] and photoelectron spectroscopy[226].



The cycloreversion of 1,3-dithietanes in the synthesis of heteroallenes containing the thiocarbonyl group is of special preparative interest. The dimers of thioketenes are, however, often insufficiently volatile to be cleaved thermally[227]. An exception is provided by the preparation of the highly reactive bis(trifluoromethyl)thioketene **148** in 70% yield from its dimer[228].

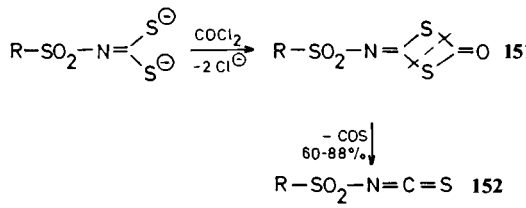


Very often useful as thioketene equivalents are 4-alkylidene-1,3-dithietan-2-ones **149** prepared by reaction of alkene-1,1-dithiolates with phosgene, and they provide access to products with various substituents[132,169,229]. Fragmentation to the thioketene, however, has only been substantiated for **149c**[227]. In the usual trapping reactions the added nucleophiles do not appear to react with the free **150** but first with **149**, and carbonyl sulfide is subsequently lost from the adduct[229d].



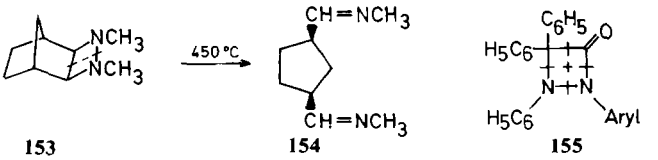
a, $R^1=CN$, $R^2=CO_2CH_3$; **b**, $R^1=CN$, $R^2=CO_2C_2H_5$; **c**, $R^1=R^2=CN$; **d**, $R^1=CH(CH_3)_2$, $R^2=CN$; **e**, $R^1=C(CH_3)_3$, $R^2=CN$

Analogous to **149**→**150** the strongly electrophilic sulfonyl isothiocyanates **152** can be liberated from the dithietanones **151**, and are stable enough to be characterized[230].

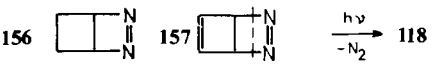


3.4.3. 1,2-Diazetidines and -Diazetines

1,3-Bismethylimino compounds **154** are the products of the flash thermolysis of **153**, in which the relatively weak NN-bond is cleaved regioselectively[231]. The norbornene analog of **153** forms the cyclopentene derivative in the same type of reaction. In the 1,2-diazetidin-3-ones **155**, on the other hand, products of both possible fragmentation pathways are observed[232].

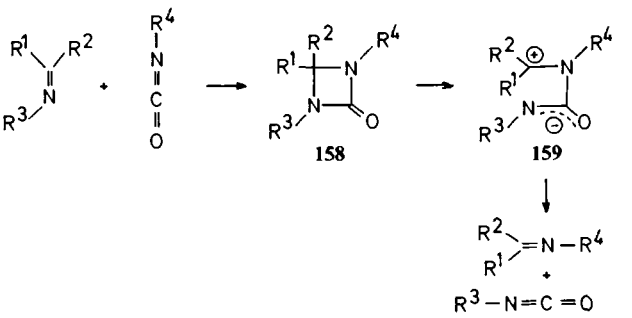


In Δ^1-1,2-diazetines, with the exception of bicycle **156**[233], electrocyclic ring opening is less likely than [2+2]-cycloreversion[28,67,234]. Photolysis of **157** is thus a way to prepare cyclobutadiene **118**[235]. Analogously, azacyclobutadiene can be produced as demonstrated on the basis of its cycloreversion products[200b].

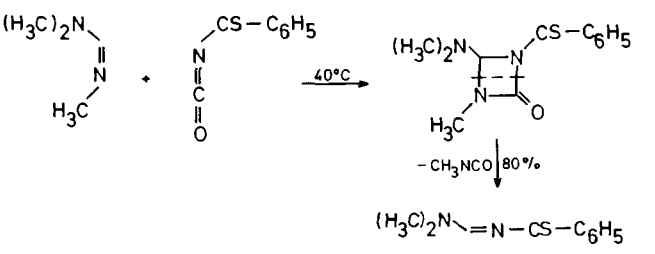


3.4.4. 1,3-Diazetidines

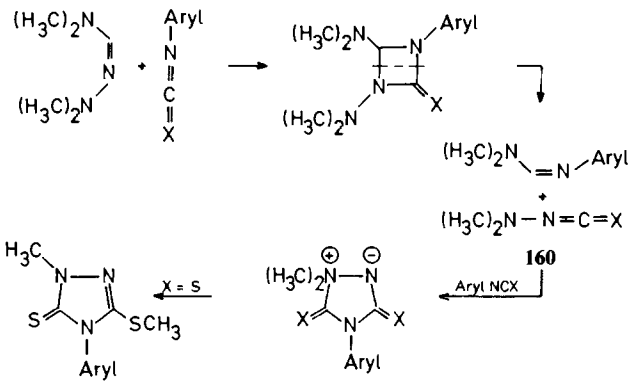
Ingold et al. found that azomethines can dimerize to produce 1,3-diazetidines, which undergo cycloreversion when warmed[236]. With 1,3-diazetidin-2-ones **158** ring cleavage is so favored that it usually occurs *in situ* during preparation from a C=N component and an isocyanate. This is especially true for cases in which R^1 or R^2 can stabilize a positive charge formed in the step **158**→**159**. Especially favorable starting materials for the reaction with isocyanates are therefore imido esters[237], amidines[238], guanidines[11,229d,239], and isothioureas[240]. A C=N compound and an isocyanate are isolated as products, so that this represents an example of an "exchange reaction" (cf. Section 1).



The method is important for preparation of C=N products with electron withdrawing groups R^4, since in this case other methods often fail; formation of **158**, however, is favored because of the high reactivity of the isocyanate component. Using this method *N*-thiobenzoylformamidines can be prepared[239].

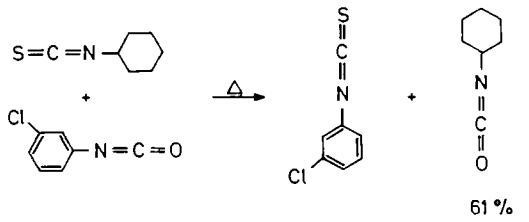


Unusual isocyanates can also be prepared by cycloreversion of **158**. Thus, starting from *N*-(α-pyridyl)azomethines ($R^3 = \alpha\text{-}C_5H_4N$) α-pyridyl isocyanate is formed, which as a highly reactive heteroallene reacts further with the starting isocyanate to give a 1 : 1 adduct[241]. With *N,N*-dimethylhydrazones, isocyanates react *via* **158** to the interesting dimethylamino isocyanate **160a**, which may be trapped as the betaine **161a**[242]. Dimethylamino isothiocyanate **160b** is also formed according to this scheme starting from phenyl isothiocyanate, which here undergoes the relatively uncommon (cf. Section 3.5.3) cycloaddition involving the C=N bond.



a, X = O; **b**, X = S

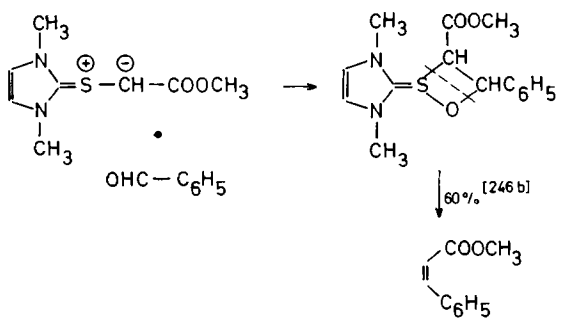
If the starting material serving as the C=N component for **158** is part of a cummulative double bond system, heterocycles **158** having sp^2-hybridization at C-4 are formed; isocyanates and isothiocyanates[243] or carbodiimides and isocyanates[244,256] react *via* exchange of substituents to give an equilibrium mixture. If one of the four participating heteroallenes has a markedly lower boiling point than the others, it can be isolated from the mixture by distillation[243b].



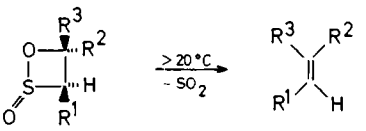
3.5. Heterocycles With Two Different Heteroatoms

3.5.1. 1,2-Oxathietanes

Sulfur ylides do not normally react with carbonyl compounds to give olefins but give oxiranes by methylene transfer[245]. There are, however, cases in which alkene formation is at least a competing reaction[246]; 1,2-oxathietanes are plausible intermediates.

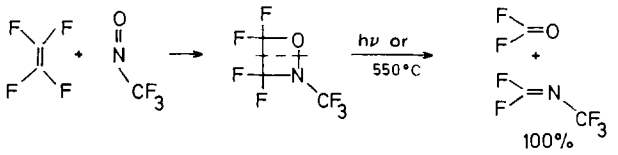


Decomposition of 1,2-oxathietane 2-oxides ("β-sultines") also leads to alkenes; the best yields in this stereospecific reaction are given by trisubstituted systems[62,63].

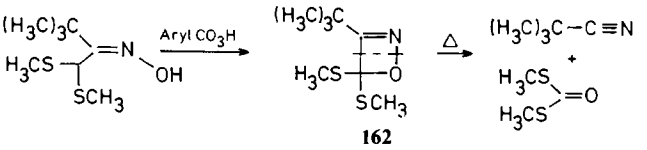


3.5.2. 1,2-Oxazetidines

[2+2]-Cycloadducts of nitroso compounds with alkenes[247], ketenes[248], or ketenimines[249] contain the easily broken NO bond. Usually, cycloreversion occurs on heating, but photochemical excitation can also lead to ring cleavage[247c].

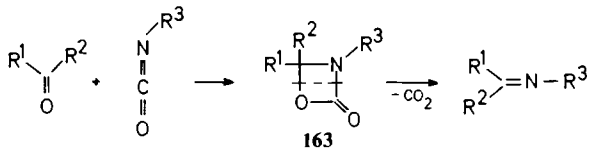


In principle, cycloreversion of 4*H*-1,2-oxazete **162** occurs in the same way, thus confirming the suggested structure[250].



3.5.3. 1,3-Oxazetidines

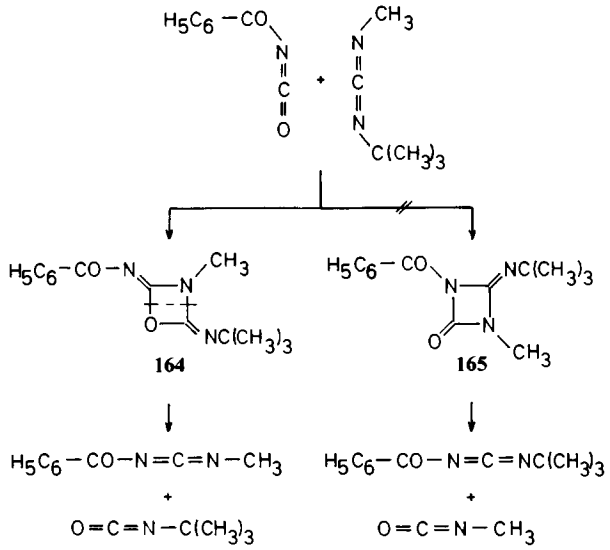
Aldehydes, non-enolizable ketones, amides, and anhydrides react with isocyanates with exchange of the carbonyl for an imino group[10]. As intermediates, 1,3-oxazetidin-2-ones **163** are plausible.



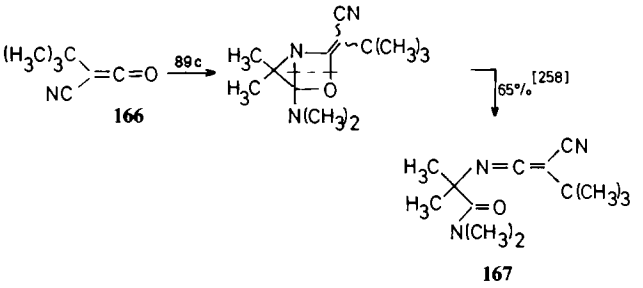
The reaction with isocyanic acid where $R^3 = H$ was even observed by *Liebig* and *Wöhler*[251]. Since the cycloaddition step is favored by increased electrophilicity in the isocyanate, acyl isocyanates[252], arenesulfonyl isocyanates[189,253], and especially chlorosulfonyl isocyanate[254] react under very mild conditions. When catalyzed by 3-phospholene 1-oxides, cycloaddition between two isocyanate molecules can be achieved, thus making carbodiimides available in good yields[255].

The [2+2]-cycloadduct from benzoyl isocyanate and *tert*-butyl(methyl)carbodiimide is thermally cleaved to afford *tert*-butyl isocyanate and an acylcarbodiimide. Therefore, the four-membered ring should be formulated as 1,3-oxazetidine **164**, and the earlier proposed 1,3-diazetidine structure **165**, from which methyl isocyanate would have

to be formed, is excluded[256]. This example demonstrates how useful the [2+2]-cycloreversion is in proving the structure of cycloadducts of unsymmetrical heteroallenes, which is often very difficult by spectroscopic methods. It remains open *a priori* which of the two π-bonds will react with a specific cycloaddition partner, *i.e.* what the *toposelectivity*[257] of the cycloaddition is.

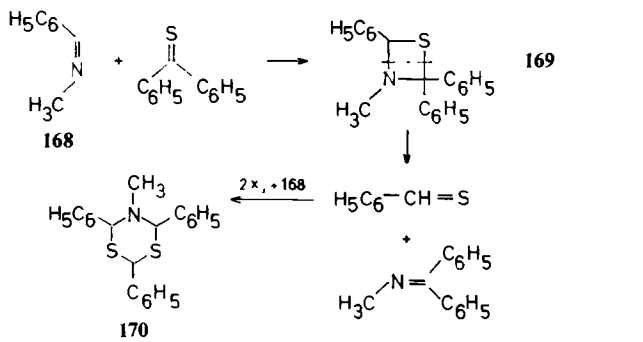


While ketenes normally react with C=N compounds *via* their C=C bond, in the reaction with the strained aminoazirines **89c—e** cycloaddition takes place primarily on the C=O part of the heteroallene[258]. *tert*-Butyl(cyano)ketene **166** reacts with **89c** in this way to form a bicyclic 1,3-oxazetidine, which undergoes *in situ* cycloreversion to the interesting ketenimine **167** containing additional functional groups.

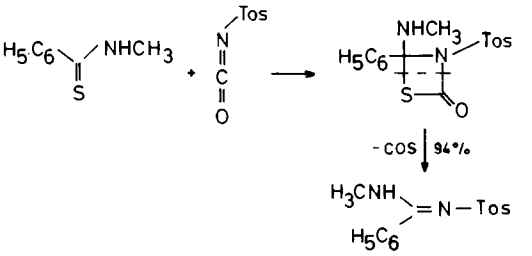


3.5.4. 1,3-Thiazetidines

Thiobenzophenone adds photochemically to benzylidene(methyl)amine **168** to afford a 1,3-thiazetidine derivative **169**, which liberates thiobenzaldehyde *via* cycloreversion. This highly reactive thiocarbonyl compound, incapable of existence in its free form, reacts essentially with unreacted **168** to give the 2:1 adduct **170**[259].

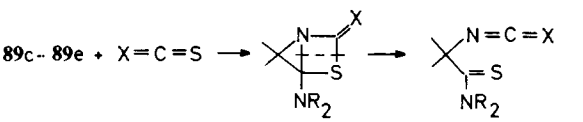


1,3-Thiazetidines also result from thermal reactions, if the imino or the thiocarbonyl group is part of a cumulative system. The four-membered ring compounds then contain at least one sp^2-hybridized ring carbon atom and easily undergo cycloreversion. Thus, exchange of a thiocarbonyl for a tosylimino group is achieved[260].



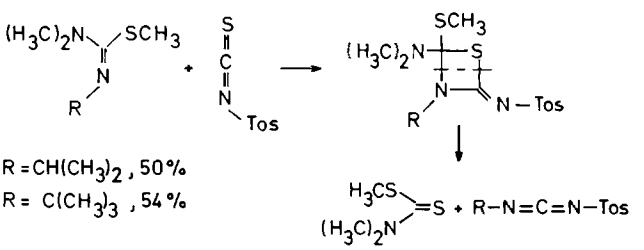
Since the reaction of carbonyl compounds with isocyanates affords imino compounds in the same manner (cf. Section 3.5.3), and the sulfur derivatives must normally be prepared from the corresponding carbonyl compounds, this procedure is generally of no preparative significance.

Interesting applications, however, are found for the cycloreversion of 1,3-thiazetidines available from thiocarbonyl-containing heteroallenes such as carbon disulfide, thioketenes, and isothiocyanates, which often react with imines toposelectively[257] at the C=S bond[10]. This occurs particularly for reactions with the strained C=N bond of the aminoazirines **89c—89e**. As already discussed in Section 2.5 for carbon disulfide (X=S, **89**→**93**) and carbon diselenide (X=Se), new heteroallenes which contain a thiocarbonyl group are obtained from thioketenes ($X=CR_2$)[129] or isothiocyanates (X=N—R)[261,262].



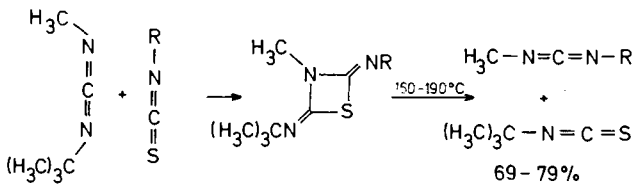
93, X = S
171, X = CR_2
172, X = NR

An example of an *in situ* cycloreversion of a 1,3-thiazetidine obtained from an acyclic C=N component is the reaction of isothioureas with benzoyl or tosyl isothiocyanate. In this case carbodiimides are formed, which, because of the electron withdrawing substituents, demonstrate high reactivity as electrophiles[263].



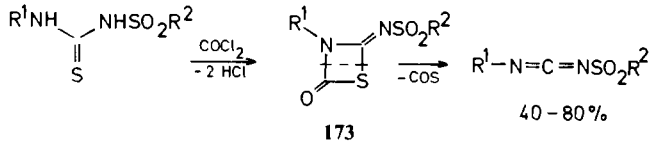
Reaction of two heteroallenes one containing a thiocarbonyl and the second an imino group usually leads *via* a

1,3-thiazetidine to an exchange reaction. The cleavage products produced establish the constitution of the primary heterocycle and in the following case permitted correction of an earlier structural proposal derived from a different toposelectivity in the isothiocyanate[256].



Depending upon substitution, 2,4-bisimino-1,3-thiazetidines can also fragment to the starting compounds[264]. Products of the cycloaddition of carbodiimides **172** and isocyanates do not undergo subsequent cycloreversion but instead zwitterionic addition products or 1:2 adducts are isolated[264].

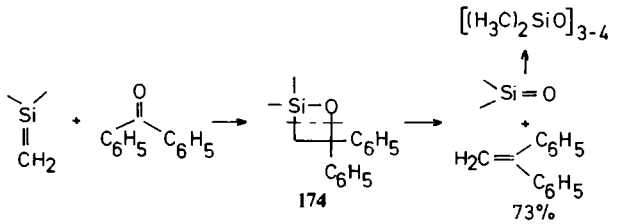
A preparatively useful approach to carbodiimides is the cycloreversion of 4-imino-1,3-thiazetidin-2-ones **173**, which can be viewed as the formal cycloadducts from isocyanates and isothiocyanates but which are available in a simpler way from thioureas and phosgene[265]. This also represents another method for preparation of sulfonylcarbodiimides[266].



173

3.5.5. 1,2-Oxasiletanes

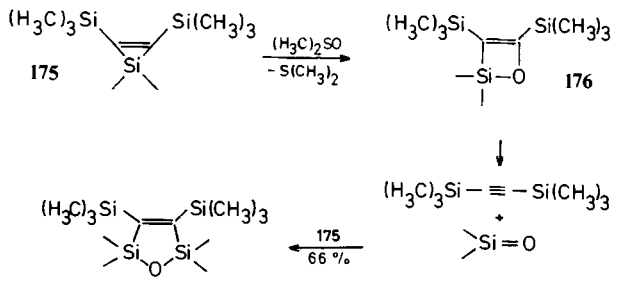
[2+2]-Cycloreversion as a simple method for conversion of a σ- into a π-bond should lead in the case of 1,2-oxasiletanes such as **174** to silanones, which because of the poor overlap of the *p*-orbitals, have a very energy-rich Si=O bond. Because of this special interest in the bonding relationships in silanones, several routes to four-membered rings containing Si—O bonds have been developed. Thus it has been demonstrated that 1,2-oxasiletanes are very unstable and spontaneously fragment to silanones[269]. If no suitable trapping agent is added then the Si=O compounds oligo- or polymerize to siloxanes.



174

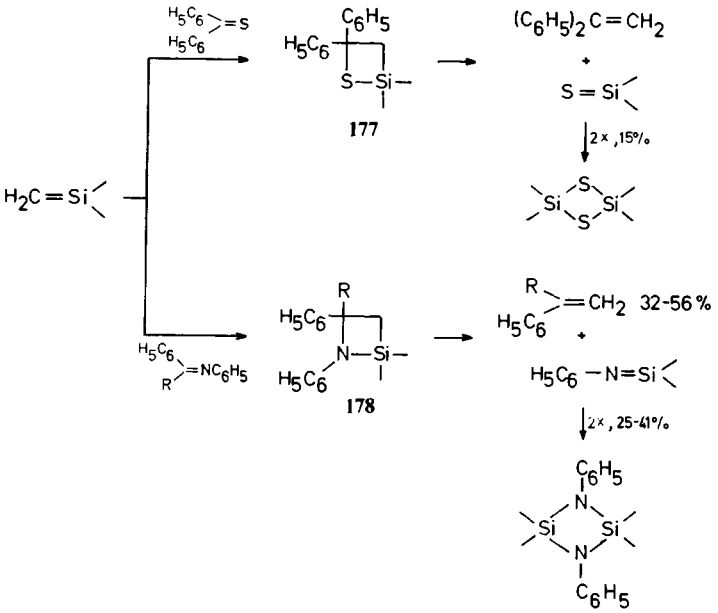
Often the 1,2-oxasiletanes are themselves formed in trapping reactions. Besides the reaction of silandiylenes (silylenes) with epoxides[267] or the intramolecular stabilization of siloxycarbenes[268] one should note especially the [2+2]-cycloaddition of silaalkenes, produced as described in Section 3.3.4, with non-enolizable carbonyl compounds. Benzophenone reacts in this way quite smoothly[270].

In the oxidation of silirene (silacyclopropene) **175** the first product is a 1,2-oxasilete **176** which does not undergo electrocyclic ring opening but reacts further in a cycloreversion step[271].



3.5.6. 1,2-Thiasiletanes and 1,2-Azasiletidines

In the same way that silaalkenes (cf. Section 3.3.4) can be trapped with carbonyl compounds (cf. Section 3.5.5), [2+2]-cycloadditions occur with thioketones or azomethines. In this way thermolabile 1,2-thiasiletanes **177**[272] or 1,2-azasiletidines **178**[273] are formed which react further in cycloreversions to give compounds with Si=S or Si=N bonds, respectively. Stabilization occurs most simply by dimerization.



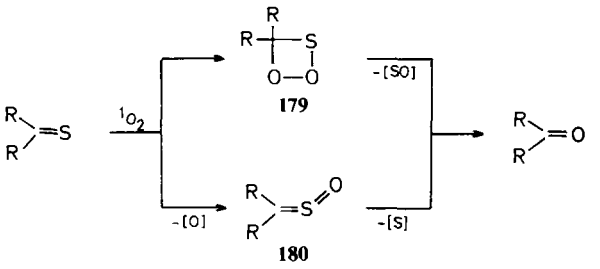
A decomposition analogous to that of **174**, **177** and **178** is observed for the corresponding germanium compounds[274].

3.6. Four-Membered Rings with Three Heteroatoms

Thioketones are desulfurized by singlet oxygen to the corresponding carbonyl compounds[275]. According to theoretical calculations a 1,2,3-dioxathietane intermediate **179** is formed which is stabilized by [2+2]-cycloreversion[276]. Alternatively, the pathway *via* a thioketone oxide **180** should be considered, especially since compounds of type **180** can be isolated starting from thioketenes[277].

Reactions of S=O or S=N systems with C=O or C=N compounds can also be explained by cycloaddition

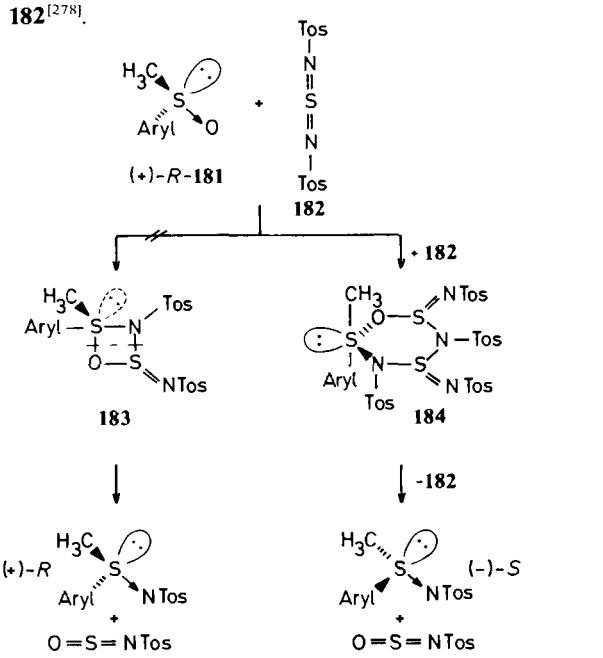
to a four-membered ring with three heteroatoms, followed by cycloreversion. However, a mechanistic study of a related example by *Cram et al.* indicated an intermediate



179

180

184. The optically active sulfoxide **181** reacted with the sulfur diimide **182** with inversion rather than retention as would be expected for the reaction *via* **183**. Furthermore the reaction is second order in the concentration of **182**[278].



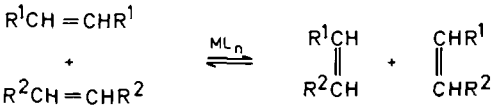
Aryl = 4-$CH_3C_6H_4$

Preparative aspects of the cycloaddition of sulfinylamines and sulfur diimides have been reviewed by *Kresze* and *Wucherpfennig*[279].

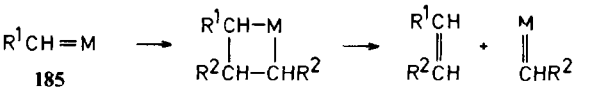
4. Related Reactions

4.1. Metathesis Reactions of Alkenes

The transition-metal catalyzed substituent exchange of olefins can be interpreted in terms of [2+2]-cycloaddition and -reversion processes.



Mechanistic studies, however, have demonstrated participation of metal-carbene complexes of type **185** and a metalacyclobutane intermediate **186**. Thus the overall reaction is a very complex process in which cycloreversion of **186** constitutes only one step[280].

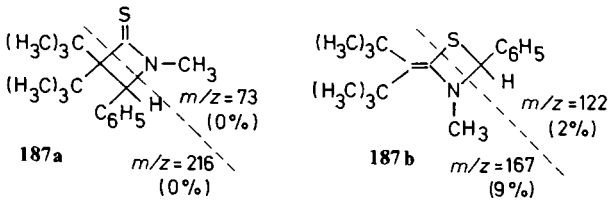


185 **186**

4.2. Electron-Impact-Induced Cycloreversions

During decomposition of four-membered ring compounds in the mass spectrometer, [2+2]-cycloreversions play an important role. This has been extensively observed for 2-azetidinones[281]. Consequently, the mass spectrum might rapidly provide information on the expected regioselectivity of preparative cycloreversions of four-membered ring compounds by thermolysis or photolysis. In fact, there appear, on the basis of theoretical considerations, to be analogies between electron-impact, photochemical, and thermal fragmentation[282]; on the other hand, however, this relationship has been placed in doubt[283]. Here too, one must expect surprises in some instances.

As a method of structure determination, electron-impact fragmentation of four-membered ring compounds can in some circumstances lead to errors. Thus, thioketenes and azomethines form 1:1 adducts, which on the basis of IR and ^{13}C-NMR data as well as decomposition reactions should doubtless be formulated as 2-azetidinethiones (e.g. **187a**) rather than thiazetidines (*e.g.* **187b**)[284]. In the mass spectrum of **187**, besides fragmentation to the starting materials, thioketene (57%), and azomethine (8%), no signals resulting from the alternative, expected fragments, methyl isothiocyanate and 2-*tert*-butyl-3,3-dimethyl-1-phenyl-1-butene are observed. On the other hand a signal is observed at $m/z = 167$, which appears to result from **187b**[284a]. Thus, under the experimental conditions (70 eV) isomerizations may occur which place in doubt the validity of mass spectra to distinguish between isomers such as **187a** and **187b**.



187a **187b**

5. Summary and Prognosis

The review has shown that [2+2]-cycloreversions are involved in many diverse areas of organic chemistry. The range runs from primarily mechanistic research on hydrocarbons *via* their use in heterocyclic synthesis and to natural product chemistry. A well-defined and therefore preparatively valuable pathway is taken by [2+2]-cycloreversions, especially if one fragment is thermodynamically quite stable. In this context aromatic compounds (*e.g.* **110**→**111**), nitrogen (*e.g.* **157**→**118**), carbon dioxide (decomposition of **132**) and carbonyl sulfide (*e.g.* **149**→**150**, **151**→**152**) are included, whereby in the last three cases the volatility of the products make the reversion irreversible, and work-up is facilitated. In these examples formation of

fragments with a labile π-bond is possible. The potential of this reaction principle is far from exhausted. Also valuable is the often high stereoselectivity of these cycloreversions.

Perhaps even more important is the [2+2]-cycloreversion of four-membered rings which form part of a bi- or polycyclic system. Conversion of the aminoazirines **89c**—**89e** into compounds such as **93**, **167**, **171**, or **172**, as well as ring opening of the tricycle **104** provide examples. In future, further interesting uses for the preparation of bifunctional compounds and for ring expansions are to be expected.

The influence of metal- and acid-catalysis on the fragmentation of four-membered rings has so far been extensively studied only with carbocycles. It appears promising for preparative purposes and from the standpoint of solar energy storage to study catalysis in the fragmentation of heterocycles, to increase the yields of known reactions, as well as to broaden the scope of [2+2]-cycloreversions.

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[1] R. B. Woodward, R. Hoffmann, *Angew. Chem. 81* (1969) 797; *Angew. Chem. Int. Ed. Engl. 8* (1969) 781.
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Synthesis and Reactions of 4-Chromanones

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Dedicated to Professor H. Grünewald on the occasion of his 60th birthday

Many natural products, such as the plant insecticides rotenone and ageratochromene (precocene), some fungitoxic phytoalexins, hashish constituents, vitamin E, and plant pigments, contain the chroman ring system as common structural unit. Some years ago we discovered a particularly simple entry to this class of heterocyclic compounds: The condensation of *o*-hydroxyacetophenones with aliphatic aldehydes and ketones in the presence of pyrrolidine leads to 4-chromanones in good yields. The scope of application and limitations as well as modification of this versatile synthesis are outlined; the accompanying tables give a good indication of the wealth and variety of possible substituents. The reaction of *o*-hydroxyacetophenone, *e.g.* with glyoxylic acid or with α,β-unsaturated ketones, proceeds atypically. The majority of the new chromanones can be used, *inter alia*, for the preparation of chromones, chromenes and chromans, and for the synthesis of tricyclic and larger ring systems.

1. Introduction

Benzopyran compounds[**] are widespread in nature and are found in a variety of forms. Many of them have interesting properties, particularly those belonging to the plant pigments (anthocyanins and flavones) and the biologically active substances, such as the psychotropic constituents of hashish (tetrahydrocannabinol), the insecticidal ageratochromenes (precocenes) and rotenone, fungicidal phytoalexins, vitamin E, as well as coumarin and catechin.

This class of compounds has therefore long been the subject of numerous intensive studies; the many-sided interest shown in such compounds equates directly with an

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[**] In Chemical Abstracts, 4-chromanones have for a number of years been referred to as 2,3-dihydro-4*H*-1-benzopyran-4-ones. In this review article we use the IUPAC nomenclature (Rule B-2.12).

advanced state of the art in their syntheses[1]. Nevertheless, many of the methods adopted (see also Section 2.5) leave much to be desired: In some cases variation of the educts is limited, in others severe reaction conditions prevent the synthesis of chromans bearing sensitive substituents. Therefore, new syntheses overcoming these disadvantages are, as in the past, very welcome.

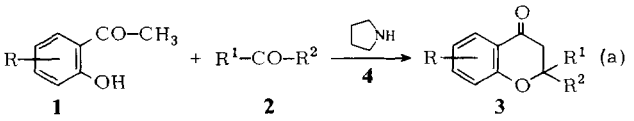
During an investigation[2] of the reactions of *o*-acylphenols with enamines we found that *o*-hydroxyacetophenones **1** undergo cyclization on reaction with aliphatic aldehydes and ketones **2** in the presence of pyrrolidine **4** to give the 4-chromanones **3**[3,4]. This reaction is suitable for the synthesis of a wealth of variously substituted derivatives, since the mild conditions enable reaction of educts containing labile groups. Moreover, because of its simplicity, the synthesis can easily be carried out on a larger scale. It thus opens up the desired entry to new chromans, and frequently provides a useful or better alternative method for the synthesis of known benzopyrans. In the following article the preparative utility of the method and the scope and limitations of the reaction are outlined with the aid of some model examples.

2. Synthesis of 4-Chromanones

2.1. Pyrrolidine-Catalyzed Syntheses

o-Hydroxyacetophenones **1** react with aliphatic aldehydes and ketones **2** in the presence of pyrrolidine **4** to give 4-chromanones **3** [eq. (a)]. Table 1 contains some examples of 4-chromanones **3**, so selected as to demonstrate the scope of possible variation of the substituents[49].

In the simplest model, a mixture of **1**, **2**, and **4** in the ratio of about 1:1:0.5 in toluene is allowed to stand for a while and then heated to boiling in an apparatus fitted with a water separator. The yield is *ca.* 60—90%. Small amounts—usually less than 15%—of 4-pyrrolidinochromenes **34** (cf. Section 2.3.3) are formed at the same time. Therefore, to increase the yield the reaction mixture is hydrolyzed with dilute hydrochloric acid before further work-up and the end products are isolated by distillation or recrystallization[3].



1 **2** **3**

Table 1. 4-Chromanones **3** prepared according to eq. (a).

	R	R^1	R^2	Yield [%]	M.p. [°C] B.p. [°C/torr]
3a	H	H	$CH(CH_3)_2$	93	125/0.07
3b	H	H	$C(CH_3)_3$	78	54-56 [5]
3c	H	H	*n*-C_9H_{19}	79	175/0.1
3d	H	H	$(CH_2)_2C_6H_5$	30	185/0.05
3e	H	CH_3	CH_3	65	88-90 [6]
3f	6-CH_3O	H	*n*-C_6H_{13}	62	53-55
3g	7-OH	—$(CH_2)_5$—		73	170-171
3h	H	—$(CH_2)_4$—		85 [a]	38-39
3i	H	CH_3	$CH(OCH_3)_2$	55 [b]	130/0.1
3k	6-OH	CH_3	$(CH_2)_2CH{=}C(CH_3)_2$	74	79-81
3l	6-Cl	CH_3	COOH	61 [c]	92-94
3m	6-OH 5,7,8-$(CH_3)_3$	CH_3	$(CH_2)_2COOH$	66 [c]	164-166
3n	6-CH_3O	CH_3	$(CH_2)_4COOH$	61 [c]	76-78
3o	H	CH_3	$(CH_2)_3$—$N(C_2H_5)_2$	75	185/0.1
3p	6-Cl	CH_3	$(CH_2)_3$—$N(C_2H_5)_2$	81	180/0.1
3q	6-CH_3O	CH_3	$(CH_2)_3$—$N(C_2H_5)_2$	66	175/0.1
3r	6-COOH	—$(CH_2)_4$—		73	229-231

[a] 86% from previously formed enamine **5** according to eq. (b) [3]. [b] Half-hours' stirring with 2N HCl leaves the acetal group intact. [c] With 1.5 equivalents of pyrrolidine (to neutralize the carboxylic acid group) in toluene, anhydrous.

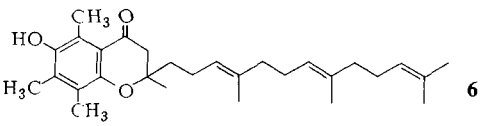
Instead of the carbonyl compounds **2** their enamines (*e.g.* **5**) obtained by reaction with pyrrolidine can also be used [eq. (b)].

This variant yields the chromanones **3** in about the same yields as according to eq. (a) if **1** and the enamine are heated in toluene or methanol[3], but it normally does not offer any advantages.

Acidic groups in **1** and **2** (carboxy- and further phenolic hydroxy groups) must be neutralized beforehand; this is best accomplished by increased addition of pyrrolidine[3] (see **3g**, **3k—n**, **3r** in Table 1).

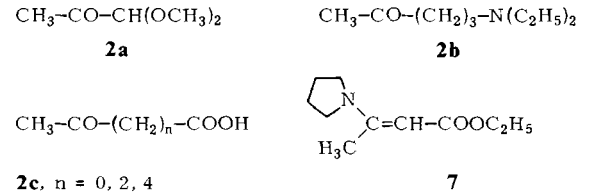
2.2. Scope and Limitations of the Reaction

Table 1 gives an idea of the scope of application of the synthesis. The mild conditions also allow the synthesis of **3** bearing labile substituents. Most of the other chromanone syntheses involve acid catalysis in the final step; *i.e.* they are unsuitable for compounds containing acid-labile groups. Thus, for example, in the case of 4-oxotocotrienol **6** the isoprenoid side-chain is cyclized in the presence of acids[7]; reaction of 2,5-dihydroxy-3,4,6-trimethylacetophenone and farnesylacetone[4] under the conditions of the pyrrolidine-catalyzed chromanone synthesis [eq. (a)] affords **6** in *ca.* 80% yield.



6

Acetal- (**2a**), amino- (**2b**) and carboxy-groups (**2c**) also remain unchanged in this synthesis. Sterically demanding moieties do not hinder reaction, as is demonstrated by the synthesis of 2-*tert*-butyl-4-chromanone **3b** (previously obtained in a four-step synthesis[5]).



Hence there is a large selection of *o*-hydroxyacetophenones **1**, and even a larger one of aliphatic carbonyl compounds available which can be employed (for exceptions see Section 2.3) in this method of synthesis.

Limitations arise where β-dicarbonyl compounds **2** form stable end products with **4**. Thus, *e.g.* the enamine **7**—a vinylogous urethane formed on reaction of ethyl aceto-acetate and pyrrolidine—no longer reacts according to eq. (b).

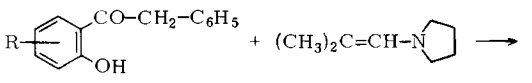
In contrast to the wide selection of **1** and **2** the basic catalyst can hardly be varied. In all cases investigated pyrrolidine proved to be by far the best catalyst; with other secondary amines (piperidine, morpholine, diethylamine) the chromanones are formed much more slowly or even not at all. This special position of pyrrolidine in enamine reactions is already well known[8,9,50].

The use of sodium hydroxide and tertiary amines (triethylamine, diazabicyclononane, *N*-methylpyrrolidine) fails, too. These observations would suggest that pyrrolidine not only reacts as base ("proton captor") but also forms intermediates in the synthesis (see Section 2.4). The relatively narrow restriction to pyrrolidine as catalyst may be the reason why this formally quite simple chromanone synthesis was first discovered as late as 1976.

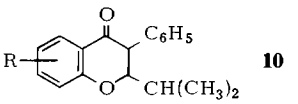
From experience it emerges that the addition of about 30—80 mol-% of pyrrolidine as "catalyst" is necessary in order to achieve satisfactory reaction. This amount can, in principle, be reduced, but at the expense of longer reaction times. It must also be taken into account that a certain amount of the base is consumed in the formation of by-products (*e.g.* 4-pyrrolidinochromenes, cf. Section 2.3.3).

Alteration of the acyl moiety in **1** has several consequences. If 2-acylphenols with longer alkyl chains are used in place of the *o*-hydroxyacetophenones the yields are drastically lowered.

If the methylene group of the acyl moiety is additionally activated, however, as for example in the phenylacetyl group, 2-isopropylisoflavanones **10** can be obtained in satisfactory yields. For this purpose **8** and **9** are heated in the absence of solvent for two to five hours at 100—125 °C. However, this reaction succeeds only with enamines formed beforehand from aldehydes; neither the free carbonyl compounds react with **8**, nor the enamines (*e.g.* **5**) derived from ketones. In **10**, the isopropyl group and the phenyl group are oriented predominantly (*ca.* 75%) in *trans* arrangement.



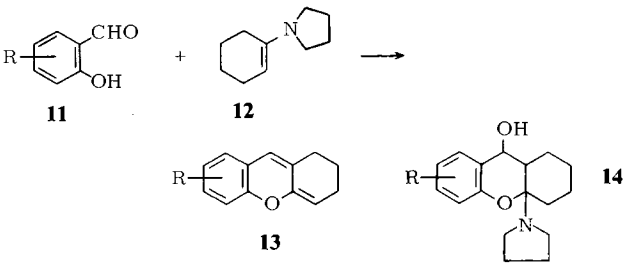
8 **9**



10

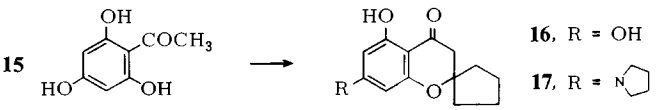
10a, R = H (81%, b.p. 170 °C/0.08 torr)
10b, R = 6-CH_3 (83%, b.p. 170—175 °C/0.1 torr)
10c, R = 7-*i*-C_3H_7O (93%, b.p. 190 °C/0.07 torr)

It should be mentioned here that salicylaldehydes **11** react somewhat differently with some enamines such as **12** derived from pyrrolidine; within relatively narrow limits the xanthenes **13**[2] are obtained, whereby the intermediary hydroxyamines **14**[10] successively split off water and pyrrolidine.



11 **12** **13** **14**

In phloroglucin one or two hydroxy groups can be replaced by other nucleophilic groups[11]. Thus, reaction of **15** with cyclopentanone in the presence of pyrrolidine does not afford the dihydroxychromanone **16** but its substitution product **17** as main product.



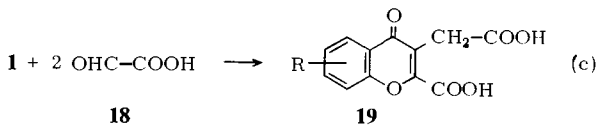
15 **16**, R = OH **17**, R = N

2.3. Special Cases

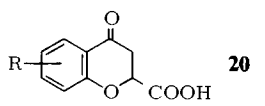
2.3.1. Glyoxylic Acid

It follows from Table 1 that oxocarboxylic acids can be readily converted into chromanones in good yields. Other than in the case of unsaturated ketones (see Section 2.3.2) it is immaterial whether both functions are adjacent (see **3l**) or separated by several methylene groups (see **3m**, **3n**).

In the case of glyoxylic acid **18**, the parent member of the oxoalkanecarboxylic acids, however, the reaction does not terminate with the primary product **20**. Addition of a second molecule of **18**, cleavage of water, and stabilization to the chromone ring system lead to the dicarboxylic acids **19** in good yields[12] (Table 2).



18 **19** (c)



20

Table 2. Dicarboxylic acids **19** prepared according to eq. (c) [a].

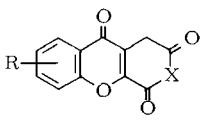
	R	Conditions	Yield [%]	M.p. [°C]
19a	H	6 d/25 °C	92	232–234
19b	7-CH_3	6 d/25 °C	64	147–148
19c	6-Cl	4 h/60 °C	78	253–255
19d	7-Cl	6 d/25 °C	84	150–152
19e	6,8-Cl_2	5 d/25 °C	66	230–232
19f	6-CH_3O	4 h/60 °C	77	219–221
19g	7,8-$(CH_3O)_2$	6 h/60 °C	80	230–232

[a] **1** and **18** are used in a stoichiometric ratio (here 1:2). **18** is neutralized with caustic soda or pyrrolidine **4** and condensation carried out with *ca.* 0.5 equivalents **4**. Water is suitable as solvent, admixed with methanol or isopropanol if necessary. Reaction is complete in 1 h at 70–80 °C; higher yields are obtained if the mixture is allowed to stand for a week at room temperature. – The acids can be precipitated from the aqueous solutions of the salts **19** with dilute hydrochloric acid.

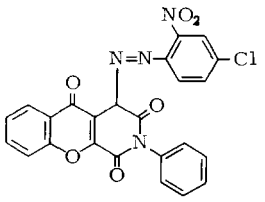
Table 3. Anhydrides **21** and imides **22** prepared from the dicarboxylic acids; **19**; yields based on **19** and **21**, respectively.

	X	R	Yield [%]	M.p. [°C]
21a	O	H	86	230–232
21b	O	6-CH_3	69	229–230
21c	O	6-Cl	83	225–227
21d	O	7-Cl	74	216–218
21e	O	7-CH_3O	79	240 (dec.)
22a	C_6H_5N	H	86	225–227
22b	4-ClC_6H_4N	H	65	225–226
22c	3,4-$Cl_2C_6H_3N$	H	70	240–243
22d	$C_6H_5CH_2N$	6-Cl	53	240–242

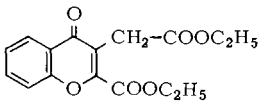
In boiling acetyl chloride (four- to eightfold excess, 10 h 25 °C, 10 h reflux) compounds **19** furnish the anhydrides **21**, from which the imides **22** can be synthesized (Table 3). Their reaction with diazonium salts[13] affords very strongly yellow-colored pigments such as **23**. Esterification of **19a** with ethanol yields the diethyl ester **24**, which has already been prepared as the sole compound of this series *via* an alternative route[14].



21, X = O
22, X = N–R^1



23

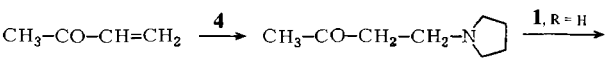


24

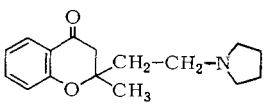
2.3.2. α,β-Unsaturated Carbonyl Compounds

The compounds **3k** and **6** show that double bonds (not in conjugation with the CO group) in the carbonyl components do not hinder benzopyranone ring-closure. However, if α,β-unsaturated aldehydes and ketones are used, the reactions take another course. We have observed two different modes of reaction.

Reaction of **1**, R = H, with methyl vinyl ketone **25** leads to formation of **27** in *ca.* 50% yield. That the primary adduct **26** functions as intermediate can be demonstrated by reaction of **25** (slight excess) with pyrrolidine **4** to give **26**[15], which reacts with **1** and further **4** to give **27**.

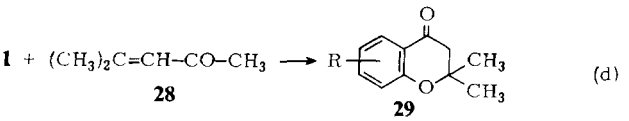


25 **26**



27

Mesityl oxide **28** behaves in a completely different manner. On reaction of **1**, R = H, with **28**, 2,2-dimethyl-4-chromanone **29a** (≡ **3e**) is formed, *i.e.* the same product as with acetone, and indeed in somewhat better yield (75% as compared with 65%). Reaction with **30** also leads to **29**. Table 4 lists some examples for **29**.



28 **29** (d)

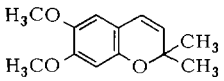
$(CH_3)_2C(OH)–CH_2–CO–CH_3$ **30**

Table 4. 2,2-Dimethylchromanones **29** prepared according to eq. (d) [a].

	R	Yield [%]	M.p. [°C]
29a	H	75	88–90
29b	6-Cl	79	[b]
29c	7-Cl	79	71–72
29d	6,7-Cl_2	63	87–89
29e	7-CH_3	69	68–70
29f	7-C_6H_5	50	98–100
29g	7-CH_3O	40	72–74

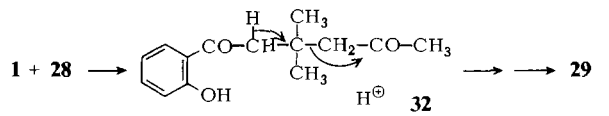
[a] **1**, **28**, and pyrrolidine are dissolved in toluene and the solution is heated to boiling for a few hours. It is then treated as in the isolation of **3** (Section 2.1) with 2N hydrochloric acid, and **29** is isolated by distillation. [b] B.p. = 110–115 °C/0.05 torr.

Both variants provide a base-catalyzed entry to the 2,2-dimethylchroman system frequently occurring in Nature. One example is the insecticidally active ageratochromene (precocene) **31**[16].



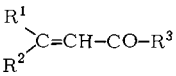
31

Presumably **29** is formed by a sequence of Michael addition (**1** to **28**) and retro-Michael cleavage (of **32**), but detailed information on the reaction is still lacking.



32

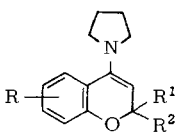
Only one of the two—in the case of **28** and **30** identical!—aldol building blocks is preserved in the final product **29**. Further experiments with unsaturated aldehydes and ketones of type **33** aimed at introduction of only the R^1—C—R^2 moiety into the chromanone met without success; either no definite secondary product could be isolated or the reaction proceeded otherwise (*e.g.* methyl vinyl ketone **25** giving **27**).



33

2.3.3. Pyrrolidinochromenes

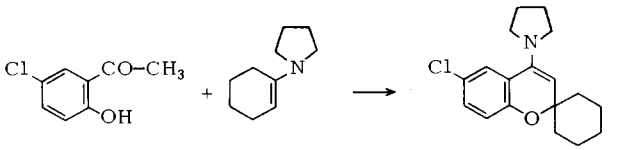
In the synthesis of the 4-chromanones according to eqs (a) and (b) a certain amount (usually less than 15%) of pyrrolidinochromenes **34** is formed as well as **3**. This side reaction is of interest, because the enamines **34** cannot be obtained from 4-chromanones **3** and pyrrolidine[17]. This



34

surprising formation of enamines **34** should therefore enable conclusions to be drawn about the course of the reaction.

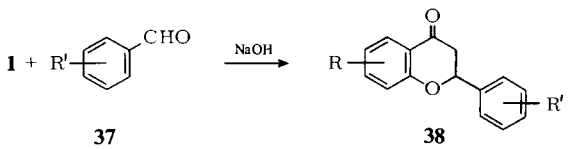
We have not investigated the formation and the amounts of the enamines **34** in detail quantitatively, since they are undesirable byproducts of the synthesis of **3** necessitating an additional hydrolysis step during work-up. In one case however—reaction of the enamine **12** with **35** in the ratio 1.1:1 in petroleum ether, 2d at 25 °C—**36** is obtained in 56% yield[18] (together with *ca.* 15% **3s**); in methanol **36** and **3s** are each formed in *ca.* 40% yield.



35 **12** **36**

2.4. Reaction Mechanism

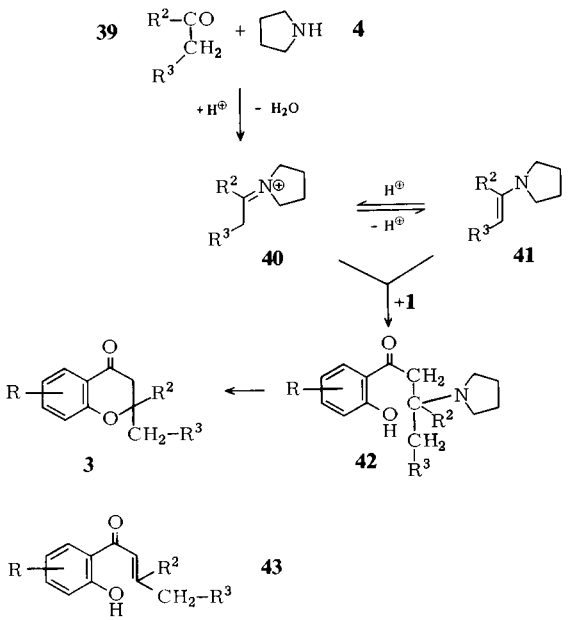
Formally, in our synthesis of chromanones from **1** and **2** only water is split off. One special case of this reaction has been known for a long time: Reaction of **1** with aromatic aldehydes **37** in the presence of caustic soda usually leads to good yields of the flavanones **38**[19]. This synthesis was



37 **38**

optimized a few years ago[20]. With the usual aliphatic aldehydes and the ketones **2**, however, these reaction conditions do not lead to the desired products; no chromanones **3** are obtained on treatment of the reaction mixture with caustic soda[3,21].

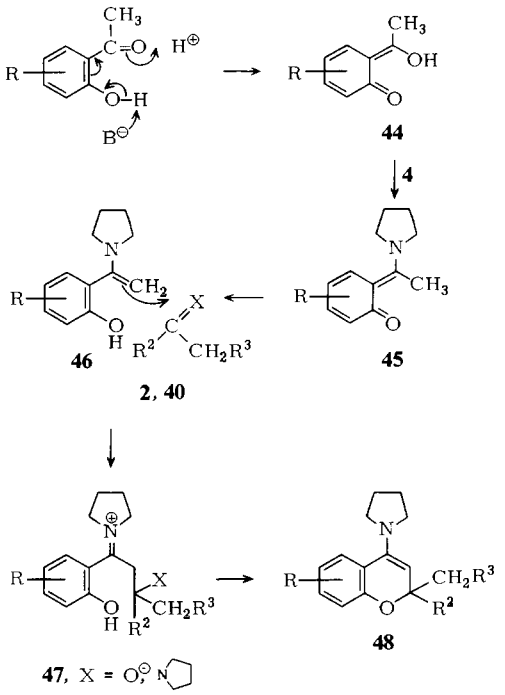
We propose the following reaction mechanism[23]: Reaction of **39** (≡ **2**, $R^1 = R^3CH_2$) with **1** leads to intermediary



Scheme 1.

formation of the addition product **42**, either *via* the enamine **41** or the alkylideneammonium ion **40** (with **1** as proton-donor). Displacement of the amine by the *o*-substituted phenolate ion—possibly after formation of the unsaturated ketone **43**—terminates the reaction to give the chromanone **3** (Scheme 1).

The ready formation of the pyrrolidinochromenes **48** (≡ **34**, $R^1 = R^3CH_2$) may be explained in terms of Scheme 2.



Scheme 2.

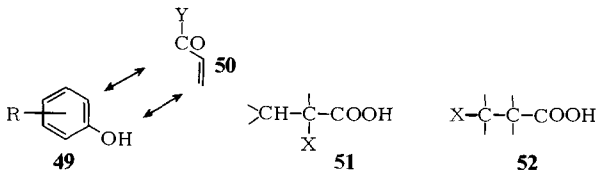
The key intermediate would then be the enamine **46** (formed from **1** and **4** *via* **44**), whose reaction with **2** and/or **40/41** would unproblematically lead *via* **47** to the end product **48**.

2.5. Other Chromanone Syntheses for Comparison

The synthesis of the chromanones according to eq. (a) extends the methods already described in the literature[24]; it enables the synthesis of a large number of hitherto difficultly accessible chromanones, and in many cases provides an advantageous preparative alternative. The following comparison with well known methods described in the literature should facilitate selection of the most suitable method of synthesis.

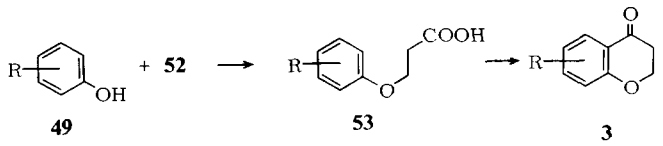
The decisive step in the majority of the chromanone syntheses described in the literature proceeds in the presence of acids (preferably polyphosphoric acid, anhydrous hydrofluoric acid[25], and methanesulfonic acid with phosphorus pentoxide[26]). In principle, a phenol **49** adds to the β-carbon atom of acrylic acids or their derivatives **50** (or their potential equivalents such as α- and β-halopropionic acids **51**, **52**), while the carboxy group acylates the arene *ortho* to the phenol group.

The most variable, and hence most frequently employed methods are: 1. The cyclization of β-phenoxypropionic acids **53**[27]; 2. The reaction of phenols with alkylated acrylic acids[28].

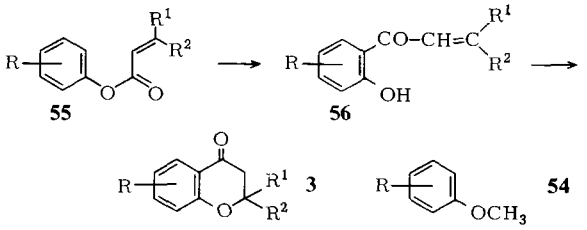


Y = OH, Halogen X = Cl, Br

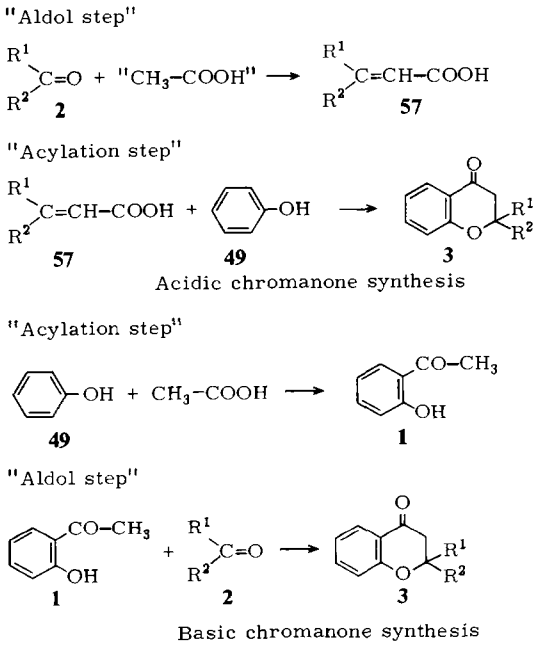
The first synthesis starts from phenols **49** and β-halopropionic acids **52**. The particular advantage lies in the possibility of obtaining C-2 unsubstituted chromanones which are not accessible *via* most of the other methods.



The second method of synthesis can be modified considerably: the phenols **49** can be replaced by their methyl ether derivatives **54**, since they are cleaved under the reaction conditions[29], and the equivalence of **50**, **51**, and **52** has already been pointed out above. Moreover, **3** can also be obtained from **55**, *via* a Fries-shift[6, 30]. The synthesis is most successful when **50**—**52** are alkyl-substituted; 2-alkyl- and 2,2-dialkylchromanones in particular, and, possibly chromanones with additional 3-alkyl groups, are readily accessible by this method. The yield is sometimes poorer because of *p*-acylation of **49**.



Both of these acid-catalyzed chromanone syntheses and the base-catalyzed chromanone synthesis according to eq.



Scheme 3. The substituents R have been omitted.

(a) are presented alongside each other for comparison in Scheme 3, in each case taking into consideration the starting material.

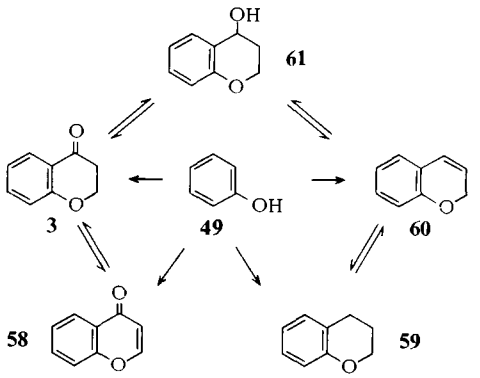
As far as this range of syntheses is comparable (in the acidic synthesis of chromanones the acrylic acids do not have to be formed only by aldol condensation!) the advantages of the base-catalyzed method are obvious: The acidic, unselective acylation step, with its restricted choice of substituents, has been placed into the synthesis of the simple and inexpensive starting materials.

3. Reactions with 4-Chromanones

3.1. Transformation into Benzopyran Derivatives with Other Oxidation States

Chroman derivatives are mainly prepared in one of two ways:

1. Conversion of a phenol **49** by annelation with a C_3- or a C_1- plus a C_2-moiety; 2. Interconversion of compounds containing a benzopyran ring system.



Scheme 4. The substituents R, R^1, and R^2 have been omitted.

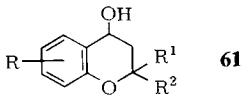
Scheme 4 presents only a few of the most important saturated and unsaturated chroman compounds with and without oxygen substitution. It shows that, *e.g.*,
the direct synthesis can be used at will in the preparation of chromones **58**, chromanones **3**, chromenes **60**, and chromans **59**, and
other benzopyrans—*e.g.* the 4-chromanols **61**—are preferably or exclusively obtained from related compounds having a benzopyran ring system.

From Scheme 4 it can also be inferred that frequently only very simple synthetic steps such as reduction, oxidation, dehydration *etc.* are required for mutual interchange between the individual classes of compounds. For this reason in chroman chemistry very often a direct synthesis with limited yields and choice of substituents is waived in favor of an overall advantageous but indirect synthesis involving several steps. In other words: Each additional entry to *one* of the benzopyran classes also indirectly increases the versatility of the others.

In this sense we have taken our chromanone synthesis according to eq. (a) as key reaction for the synthesis of some other classes of benzopyrans and have investigated the synthesis of chromanols and their direct secondary products such as chromenes, 4-halochromans, 4-aminochromans and 4-alkoxychromans in this way. Some examples are presented in the following sections.

3.1.1. 4-Chromanols **61**

4-Chromanones **3** can generally be reduced quite smoothly to the chromanols **61**. Reactions with complex hydrides ($LiAlH_4$, $NaBH_4$) are just as suitable as the catalytic hydrogenation[31]. Table 5 lists some examples. With dissimilar moieties R^1 and R^2, the compound which can be isolated in crystalline form as main product is that one in which the larger group on C-2 and the hydroxy group on C-4 are arranged equatorially.



61

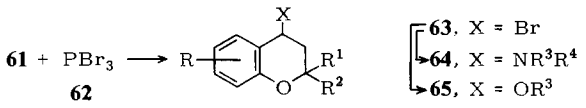
Table 5. 4-Chromanols **61** prepared by reduction of 4-chromanones **3** with $NaBH_4$.

	R	R^1	R^2	Yield [%]	M.p. [°C]
61a	H	n-C_6H_{13}	H	73	48–50
61b	H	—$(CH_2)_4$—		95	56–58
61c	H	CH_3	$(CH_2)_2$-Pyrrolidino	42	100–101
61d	6-Br	CH_3	CH_3	86	97–98
61e	6-Cl	CH_3	$(CH_2)_3$—$N(C_2H_5)_2$	88	[a]
61f	7-Cl	CH_3	CH_3	96	82–84
61g	6,8-Cl_2	—$(CH_2)_4$—		96	94–96
61h	7-C_6H_5	—$(CH_2)_4$—		69	91–93
61i	6-CH_3O	n-C_6H_{13}	H	78	66–68
61k	6-OH	n-C_9H_{19}	CH_3	75	112–115
61l	6-OH, 5,7,8-$(CH_3)_3$	3-Cyclohexenyl	H	96	198–200

[a] B.p. = 180 °C/0.2 torr.

3.1.2. 4-Bromo-, 4-Amino-, and 4-Alkoxychromans **63–65**

4-Chromanols **61** are converted with phosphorus tribromide **62** into 4-bromochromans **63**[32]. On warming, compounds **63** readily eliminate hydrogen bromide with formation of the 2*H*-chromenes **60**. The 4-aminochromans **64**[32] can be prepared by reaction of **63** with primary and secondary amines and the 4-alkoxychromans **65** by reaction with alcohols in the presence of triethylamine; the chromenes **60**, which are formed at the same time in small amounts, can easily be separated from the higher boiling end products **64** and **65** by distillation.



61 + PBr_3 → **62**

63, X = Br
64, X = NR^3R^4
65, X = OR^3

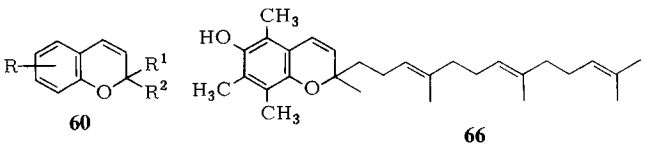
Table 6. 4-Amino- and 4-alkoxychromanes **64** and **65** (yields based on **63**; **63** obtained from **61** in *ca.* 85% yield and crude product used for further work). R^1—R^2 = —$(CH_2)_4$—, in the case of **65a**, however, R^1 = H, R^2 = $CH(CH_3)_2$.

	R	X	Yield [%]	B.p. [°C/torr]
64a	H	$N(C_3H_7)_2$	61	150/0.2
64b	H	NH—C_6H_5	55	[a]
64c	H	NH—$(CH_2)_2$—$N(C_2H_5)_2$	91	145–155/0.1
64d	6,8-Cl_2	NH—$(CH_2)_2$—OCH_3	74	160–165/0.1
64e	6-CH_3O	NH—$CH_2C_6H_5$	56	190–200/0.1
65a	H	OCH_3	79	100–105/0.1
65b	H	O—$(CH_2)_2$—OCH_3	84	140–145/0.05
65c	6-Cl	O—CH_2—C≡CH	78	135–145/0.07

[a] M.p. = 85–87 °C.

3.1.3. 2*H*-Chromenes (2*H*-Benzopyrans) **60**

4-Chromanols **61** are frequently used for the synthesis of 2*H*-chromenes **60**[16] (Table 7). The dehydration can be accomplished by treatment with acidic reagents, whereby the best conditions (*e.g.* reflux in toluene with *p*-toluenesulfonic acid or warming with hydrochloric acid in alcohols) must be ascertained in each individual case. Electron-donating moieties in the arene promote dehydration; thus, 4-hydroxytocotrienol (cf. also **6**) is already converted into 3,4-didehydrotocotrienol **66**[4] during the distillation. Attention has already been drawn to the ready formation of **60** *via* 4-bromochroman **63** (Section 3.1.2).



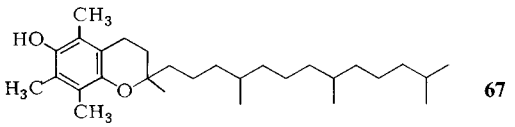
60 **66**

Table 7. Chromenes **60** prepared from 4-chromanols **61** (yields based on **61**).

	R	R^1	R^2	Yield [%]	B.p. [°C/torr]
60a	H	—$(CH_2)_4$—		92	100/0.1
60b	H	CH_3	$(CH_2)_3$—$N(C_2H_5)_2$	84	115–117/0.1
60c	6-Cl	CH_3	$(CH_2)_3$—$N(C_2H_5)_2$	81	120–125/0.06
60d	7-CH_3O	CH_3	$(CH_2)_3$—$N(C_2H_5)_2$	70	140/0.03

3.1.4. Chromans **59**

Starting from 4-chromanones **3**, the chromans **59** can also by synthesized *via* the steps **61** and **60**. We have followed this route in the case of the synthesis of vitamin E **67**[4]. More attractive would be a direct conversion of **3** into **59**. Of the known methods, however, only the Clemmensen reaction is practicable[33], while under the strongly basic conditions of the Wolff-Kishner reduction the pyran ring is opened. In the case of chromanones which do not contain any groups that are sensitive towards borane, the reaction with B_2H_6-generating agents is recommended[34]; in the combination of the adducts **68** and **69** we have found a convenient route for directly converting **3** into **59** (see Table 8)[35].



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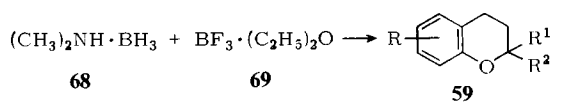


3 + $(CH_3)_2NH \cdot BH_3$ (**68**) + $BF_3 \cdot (C_2H_5)_2O$ (**69**) → **59**

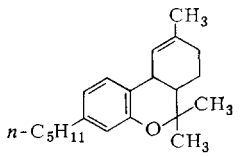
Table 8. Chromans **59** prepared by reduction of 4-chromanones **3** with **68** + **69**.

	R	R^1	R^2	Yield [%]	B.p. [°C/torr]
59a [a]	H	—$(CH_2)_4$—		82	95/0.1
59b	7-CH_3	CH_3	$(CH_2)_3$—$N(C_2H_5)_2$	90	200/0.1
59c	7-OH	CH_3	n-C_9H_{19}	65	185–190/0.1

[a] **59a** can also be obtained from dihydrocoumarin and the bis-Grignard compound prepared from 1,4-dibromobutane [51].

3.2. Higher Ring Systems

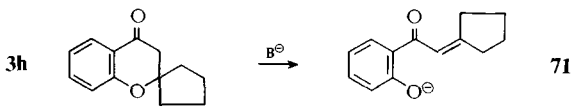
The preparative accessibility of chromane chemistry *via* chromanones **3** is also of interest for introduction of additional rings. As example we have investigated the annelation of six-membered carbocycles to C-3 and C-4 of the chroman ring system. The tricyclic systems which can thus be obtained occur, *inter alia*, in natural products such as tetrahydrocannabinol **70**.



70

Owing to the instability of the chromanones towards alkalis (example **3h**→**71**) the usual base-catalyzed reactions for such additions (Michael addition, Robinson annelation, ester condensation) occasionally proved to be of only limited use or gave unexpected products.

The sensitivity of 2-unsubstituted and 2,2-dimethylated chromans towards alkalis has been known for a long time[36,37]. However, it is only of importance when strong bases are used under severe conditions and then leads to relatively unspecific reactions. In contrast, in the case of the particular chromanones investigated by us, namely those coupled in a spiro-like fashion at C-2 or substituted with long alkyl chains, the pyran ring is particularly easily opened by the action of alkalis and, in fact, all the more rapidly and completely, the stronger the base and the more polar the solvent.



3h **71**

The free phenol **76** (m.p. 49 °C) can be obtained from **71** by careful acidification; however, it rapidly recyclizes in acids. The disadvantages of this behavior for base-catalyzed reactions are: 1) On using larger amounts of base a considerable portion of the chromanone molecules are cleaved and undergo recyclization during the usual acidic work-up; this portion has then apparently "not reacted"; 2) the base considered as catalyst is "consumed" as phenolate of type **71** and thus cannot fulfill its purpose.

3.2.1. Michael Addition and Robinson Annelation

Robinson annelation has proven particularly suitable for the addition of a six-membered carbocycle to C-3 and C-4 of the chroman ring system[38,39]. Attempts to obtain the tricyclic chroman derivative **73** in a one-pot reaction gave unsatisfactory results. Therefore, on the basis of known examples given in the literature, we attempted a stepwise procedure with isolation of the Michael adducts **72** (Table 9).

In order to circumvent the problem of not being able to achieve selective monoaddition of methyl vinyl ketone **25**, we have tried the reversible formylation of **3** before the addition[40]. Such a methodology *via* **74** and **75** is also

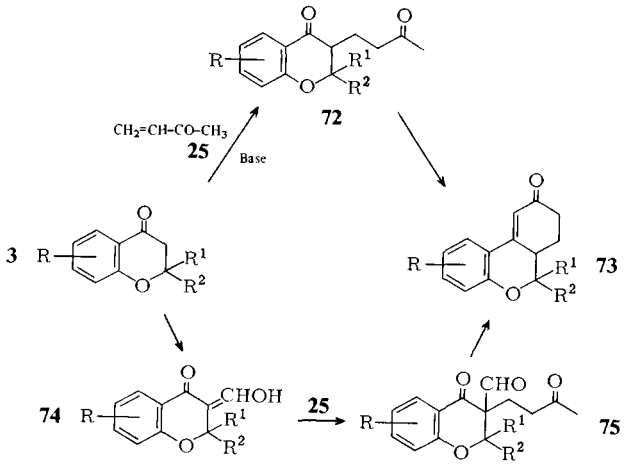


Table 9. 3-γ-Oxobutyl-4-chromanones **72** and 6a,7-dihydro-6*H*-dibenzo[*b*,*d*]pyran-9(8*H*)-ones **73**.

R	R^1	R^2	72 [a] Yield [%]	72 [a] B.p. [°C/torr]	73 [b] Yield [%]	73 [b] M.p. [°C]
H	H	C_3H_7	23	165–170/0.5	68	98–99
H	CH_3	CH_3	32	120–125/0.2	78	75–77
H	—$(CH_2)_4$—		72	158–167/0.14	84	121–123
H	—$(CH_2)_5$—		68	160–170/0.2	78	101–103
7-OCH_3	CH_3	CH_3	25	155–160/0.1	60	103–105
6-Cl	CH_3	CH_3	39	135–140/0.1	58	100–102
7-OCH_3	—$(CH_2)_4$—		52	160–165/0.2	36	105–107
6-Cl	—$(CH_2)_4$—		51	170–175/0.1	63	122–123
6-CH_3	—$(CH_2)_4$—		65	155–165/0.2	75	86–87

[a] Yields (based on **3**) determined gas-chromatographically. Two thirds or more can be obtained pure by distillation; less pure educts also suffice for the cyclization to **73**. [b] Yields based on **72**.

known from chroman chemistry[41,42], but, for the reasons outlined in Section 3.2.2, it cannot be carried out with a number of strongly alkali-labile chromanones.

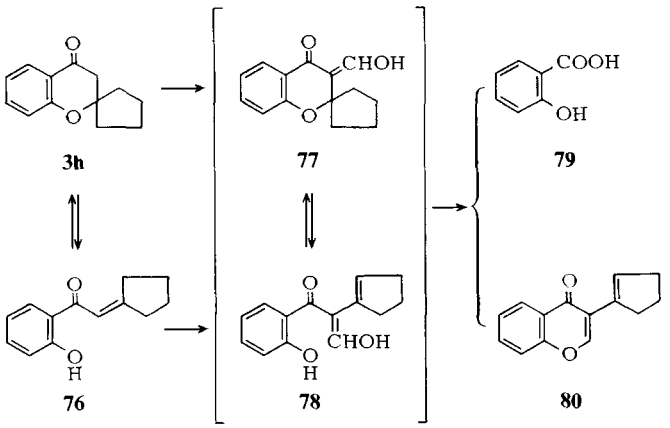
Consequently, in the cases of interest to us we were compelled to search for empirical conditions under which the chromanones **3** are preferably monoalkylated. Strong bases such as sodium hydride, sodium alkoxide, and benzyltrimethylammonium hydroxide mainly proved to be of little use; diazabicyclononene (DBN) and diazabicycloundecene (DBU), on the other hand, were found to be suitable reagents for promoting monoalkylation, particularly when used in the presence of only small amounts of solvent and a large excess (*ca.* fivefold) of **25** at room temperature[43]. In the case of chromanones having longer alkyl chains on C-2 or spirocyclically coupled groups the method leads to satisfactory yields of monosubstituted products. With chromanones containing small substituents (*e.g.* methyl groups) at C-2, 3-mono- and 3,3-disubstituted products are formed in about equal amounts.

The last step for the synthesis of the desired dibenzopyranones **73** (Table 9), the cyclization of the monoadduct **72**, can be achieved with $NaOCH_3$ in methanol (1d at room temperature, **72**: $NaOCH_3$ = 1:1.5, cf.[44]).

3.2.2. Ester Condensation

3-Formylchromanones **75** function as intermediates for the selective monoadditon of methyl vinyl ketone **25** to **3**. Some 2-unsubstituted and 2,2-dimethylated chromanones

have already been converted into tricyclic systems with formic acid esters under the usual alkaline conditions[45–48]. Attempts to extend this procedure to 2,2-substituted chromanones bearing larger substituents failed because of the increased sensitivity of these compounds to bases. Reaction of **3h** gave the result outlined in Scheme 5.



Scheme 5.

Besides up to 60% "unchanged" **3h**, approximately 20–25% of salicylic acid **79** and about the same amount of 3-cyclopenten-1-ylchromone **80a** are obtained. Both compounds could arise from **78**. The expected hydroxymethylenechromanone **77** has not been observed.

The synthesis of the chromones **80** proceeds markedly better with dimethylformamide acetal **82** as formylating agent than with formic acid esters; the novel (cyclo)alkenylchromones **80** are obtained in yields of up to *ca.* 50% on heating the reaction partners in the ratio of about 1:1.5 for several hours (Table 10).

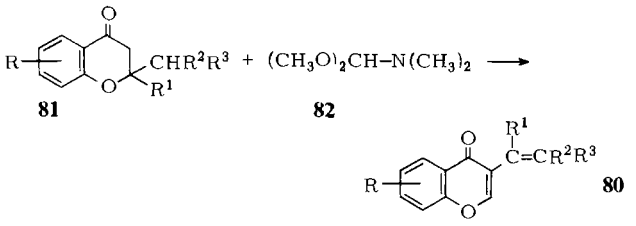


Table 10. Synthesis of 3-alkenylchromones **80** from 2,2-dialkylchromanones **81** and dimethylformamide acetal **82**.

	R	R^1	R^2	R^3	Yield [%]	M.p. [°C]
80a	H	—$(CH_2)_3$—		H	48	115–116
80b	H	H	CH_3	CH_3	47	61–62
80c	H	H	H	$C_6H_5CH_2$	28	105–107
80d	6-Cl	—$(CH_2)_3$—		H	40	156–158
80e	7-CH_3O	—$(CH_2)_3$—		H	52	139–140
80f	7-C_6H_5	H	CH_3	CH_3	53	171–173

4. Closing Remarks

The methods described here for the synthesis of chromanones (and some secondary products) can be made use of in various ways. The reaction itself, besides being of use in the synthesis of individual benzopyrans—such as well known or only recently isolated natural products (*e.g.* 6-acetyl-2,2-dimethyl-4-chromanone[49])—is, in our opinion, of paramount importance for industrial research work on active substances. Characteristically this sector of research is often oriented around naturally occurring "lead compounds"; however, for working out the optimal property-profile of the active substance, syntheses capable of greater variation are necessary. Both of these aspects—the 'natural product approach' and 'preparative flexibility'—appear to us to have been unified to a great extent in the methods presented here.

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The Reactivity of Primary Free Radicals and Radical Ions, Mass Transfer, and Electrosorption—The Fundamental Factors for Selectivity in Electrochemical Syntheses of Organic Compounds

By Hartmut Wendt*

Dedicated to Professor Leopold Horner on the occasion of his 70th birthday

In many cases the electrolytic synthesis of organic compounds is rather unselective. This is because the primary radical ions and/or radicals are very often so reactive that they are able to react competitively with several of the different species present in the electrolyte. The aim is to increase the selectivity by rationally altering the process parameters; this demands a knowledge, *inter alia*, of electrosorption effects and of the relationships between mass transfer and chemical reaction, at or in front of the electrodes (in the so-called reaction layer). Four examples will be used to illustrate this theme:

1. The anodic synthesis of triarylsulfonium salts,
2. The addition of anodically generated N_3-radicals to olefins, producing "monomeric" 1,2-diazides and "dimeric" 1,4-diazides,
3. The cathodic synthesis of optically active 1-(2-pyridyl)ethanol,
4. The synthesis of 1,2- and 1,4-diol ethers by anodic oxidation of vinyl compounds in alcoholic solutions.

1. Introduction

The view which used to be frequently expressed that the electrolytic synthesis of organic compounds should be more selective than the "normal" *i.e.* thermally activated synthetic reactions, because the (electrical) energy[**] expended at the beginning of the reaction is very exactly defined by the working potential of the electrode, is in general untrue. The minimal electrical energy required for the primary anodic oxidation or cathodic reduction of organic substrates is usually considerably higher than the free enthalpy of the overall electrochemical reaction.

This can be explained using the cathodic hydrodimerization of acrylonitrile to adipodinitrile (Baizer's synthesis):

$$2\,CH_2{=}CHCN + H_2O \rightarrow (NC{-}CH_2{-}CH_2)_2 + 0.5\,O_2 \qquad (2\,F \text{ consumed})$$

From the cathodic half-wave potential of acrylonitrile[1] and the equilibrium potential of the oxygen electrode at pH 7[2] the minimal expenditure of electrical energy amounts to *ca.* +540 kJ/mol adipodinitrile. The free enthalpy of the overall reaction given above can be roughly calculated from the reaction enthalpy of the hydrogenation

$$2\,CH_2{=}CHCN + H_2 \rightarrow (NC{-}CH_2{-}CH_2)_2$$

(−200 kJ/mol[3,4]) and the free enthalpy of decomposition of water (+240 kJ/mol[5]), at only about +40 kJ/mol adipodinitrile, which is less than a tenth of the minimum expenditure of electrical energy.

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[**] The maximal expended electrical energy can be calculated (to a rough approximation) from the difference between the foot potentials of the current-potential curves for the respective anodic and cathodic processes:

$$\Delta E^{el}_{min} \approx (U^{foot}_{anod} - U^{foot}_{cath}) \cdot nF$$

n = The number of electrons consumed per molecule
F = Faraday's constant

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The initial electrochemical reaction steps [Eqs. (1a) to (1d)] produce undesirably reactive radical ions [Eqs. (1a) and (1b)] from neutral molecules (S) or radicals [Eqs. (1c) and (1d)] from ions ($Cat^{\oplus}$, $An^{\ominus}$):

$$S + e \rightleftharpoons S^{\odot\ominus} \quad (1a)$$

$$S - e \rightleftharpoons S^{\odot\oplus} \quad (1b)$$

$$Cat^{\oplus} + e \rightleftharpoons Cat^{\odot} \quad (1c)$$

$$An^{\ominus} - e \rightleftharpoons An^{\odot} \quad (1d)$$

Because of their high energy content and high reactivity[*] these species can react further in numerous competing parallel reactions, so that at least two and often more products are formed at the same time (Fig. 1). This happens of course irrespective of whether the radicals and/or radical ions are produced electrochemically or by conventional chemical means.

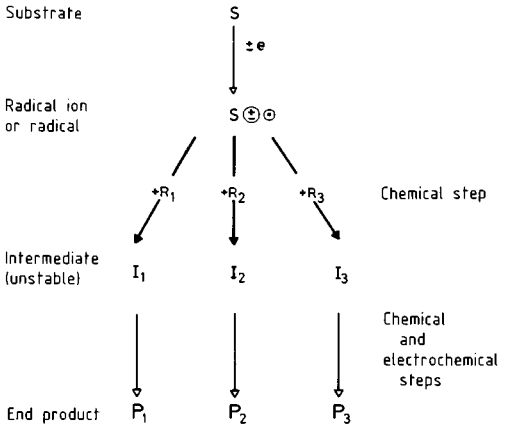

Fig. 1. Schematic representation of the reaction course from initial charge-transfer step, chemical step and further chemical steps or electron-transfer steps. The first chemical step usually determines the structure of the end-product.

Figure 2 shows seven reaction paths by which radical cations formed by anodic oxidation of vinyl compounds can react[6].

One of the aims of the synthetic chemist is to increase the selectivity of such intrinsically non-selective reactions by altering the process parameters (temperature, current density, mass transfer conditions, reactant and depolarizer concentrations *etc.*); to achieve this the rate of formation of the required product must be raised significantly above the rate of formation of the competing products.

In many closely studied examples the first chemical step [Eqs. (2a) to (2c)] which follows the primary charge transfer determines not only the structure of the end-product P_i but also the rate of its formation (r_i):

$$S^{\oplus\odot} + R_1 \xrightarrow{k_1} I_1 \rightarrow P_1 \quad (2a)$$

$$S^{\oplus\odot} + R_2 \xrightarrow{k_2} I_2 \rightarrow P_2 \quad (2b)$$

$$S^{\oplus\odot} + R_3 \xrightarrow{k_3} I_3 \rightarrow P_3 \quad (2c)$$

$$(dc_{P1}/dt)/(dc_{P2}/dt)/(dc_{P3}/dt) = r_1/r_2/r_3 \quad (3)$$

If it can be assumed that the three competing reactions are first order not only with respect to the reactants R_1, R_2, and R_3 but also with respect to the reactive primary species $S^{\oplus\odot}$ then the ratio of formation of the different products is described by Eq. (4a) (N_{P_i} = mol P_i in the product mixture):

$$dN_{P1}/dN_{P2}/dN_{P3} = k_1 c_{R1} c_S / k_2 c_{R2} c_S / k_3 c_{R3} c_S = k_1 c_{R1} / k_2 c_{R2} / k_3 c_{R3} \quad (4a)$$

If the concentrations of R_1, R_2, and R_3 do not change during the electrolysis then the same expression gives the molar ratio of the end-products of a batch electrolysis:

$$N_{Pi}/N_{Pj} = (dN_{Pi}/dt)/(dN_{Pj}/dt) \quad (4b)$$

The selectivity is defined by Eq. (4c)

$$\eta(\mathrm{i}) = \text{selectivity (i)} = N_{Pi}/\sum N_{Pj} \quad (4c)$$

Since the reactions of reactive radicals and radical ions generally exhibit low activation energies, the ratios of the rate constants $k_1/k_2/k_3$ and hence the selectivity η(i) can hardly be altered or improved significantly by changing the reaction temperature[*]. Instead, the selectivity can be influenced significantly better by changing the concentrations of R_1, R_2, and R_3. It must, however, be ensured that

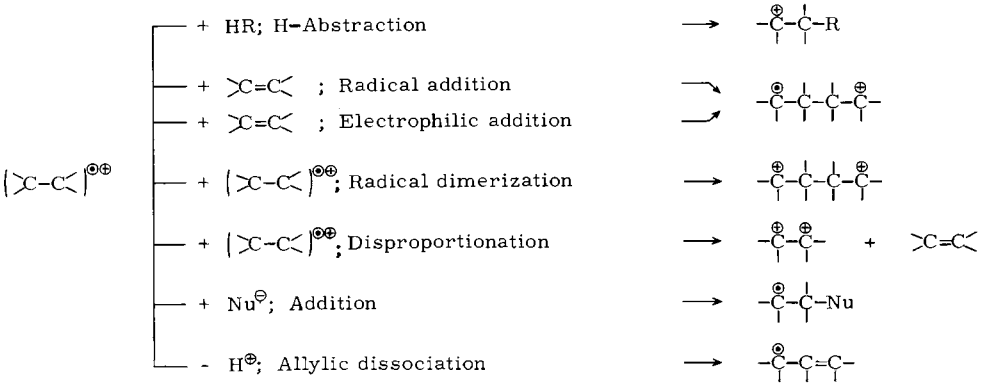

Fig. 2. Seven possible parallel reactions for radical cations, produced by anodic 1e-oxidation of vinyl-compounds. Allylic dissociations are possible only in allylic educts with a β-H atom.

[*] The cathode or anode potentials which are required to produce radical ions and/or radicals by electrochemical reduction or oxidation are an approximate measure of their reactivities [6]; the reactivity depends, additionally, on the nature of the solvent.

[*] Because of the increase in viscosity and the decrease in electrical conductivity with decreasing temperature, the working temperature cannot lie below about −50 °C.

the reactant concentrations are controlled in the "reaction zone". Due to the fast reaction of the primarily formed radicals or radical ions, this reaction zone is located in the boundary layer in front of the electrode or at the electrode surface itself. An important objective of this article is to illustrate how far the reactivity of electrolytically-produced radical ions, radicals and other short-living reactive intermediates controls the thickness of the reaction layer. This is the average distance from the electrode, reached by the reactive intermediates as a result of the competition between chemical reaction and diffusion away from the electrode surface. A knowledge of the site of reaction and details of the reaction kinetics will allow one to optimize the process *i.e.* to maximize its selectivity. If, for example, the key reaction is a surface reaction then the reaction as a whole can be controlled by manipulating the adsorption equilibria.

2. The Reactivity of the Primary Species and Control of the Reaction

2.1. The Boundary Layer Model and the Relationship between the Lifetime of the Primary Species and the Expansion of the Reaction Layer

Figure 3 illustrates the boundary layer model, while Figures 4a to 4c show schematically three cases for concentration profiles of competing reactants in the vicinity of the electrode. The basis for the calculation of such concentration profiles is the analytical or numerical solution of differential equation (5), which describes the concentration distribution of the reactant i in front of the electrode, in terms of convection (1st term), diffusion (2nd term) and reaction (3rd term), under steady-state conditions typical for a normal electrolysis. The solution of equation (5) assumes knowledge of the fluid-dynamic velocity profile in front of the electrode.

$$\frac{d(wc_i)}{dy} + D_i \frac{\partial^2 c_i}{\partial x^2} - r_i = 0 \qquad (5)$$

r_i = rate of consumption or formation of the ith species
w = linear velocity of the electrolyte (usually parallel to the electrode surface)
y = coordinate parallel to the flow vector (in most cases parallel to the electrode surface)
D_i = diffusion coefficient of the ith species

As a consequence of free or forced convection[*] owing to adhesion and viscous friction of the electrolyte in front of the electrode a fluid dynamic boundary layer of thickness δ_w develops (Fig. 3a)[**]. Due to the consumption of the depolarizer or the formation of electrolysis products, spatial concentration profiles of products or the depolarizer are built up between the electrode surface and δ_w. These profiles extend up to $0.33\delta_w$ into the solution (Figs. 3a, 3b).

If the formation of this "concentration boundary layer" is not disturbed by chemical reactions of the species under consideration, it is known as the Nernst diffusion layer of thickness δ_N. The quotient D/δ_N is the mass transfer coefficient k_m, which determines the mass transport velocity to and from the electrode.

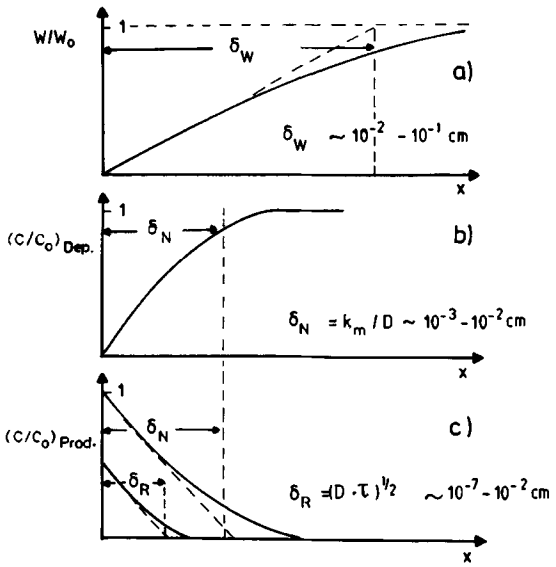

Fig. 3. Representation of the boundary layer model: a) fluid dynamic boundary layer in which a velocity profile is built up at the electrode, caused by wall-adhesion and viscosity; b) Nernst diffusion layer; c) reaction layer; with simultaneous mass transfer and chemical reaction of the primary species the concentration profile in the reaction layer is contracted from δ_N to δ_R. w = linear velocity of the electrolyte, w_0 = velocity in the bulk electrolyte, c = concentration, c_0 = arbitrary reference concentration, k_m = mass transfer coefficient, Dep. = depolarizer, D = diffusion coefficient, τ = half-life of the primary species.

If the species under consideration reacts with other species of the electrolyte during transport to the electrode (depolarizer) or, if it is produced at the electrode, and undergoes reaction on transfer from the electrode into the bulk of the solution, then the concentration profiles resulting from diffusion and convection alone will be contracted, if the reaction velocity is high enough. In particular the rapid consumption of primarily formed species by chemical reaction results in

a) a significant decrease in the spatial extension of the respective concentration profile
b) a decrease in the concentration of the respective species at the electrode (Fig. 3c)[7-9, 12].

A distinction then has to be made between the thickness δ_N of the Nernst diffusion layer—defined in terms of convective diffusion only—and the generally much thinner reaction layer thickness δ_R, which is determined by the competition between chemical reaction and diffusion. δ_R can be estimated using Eq. (6)[*] if the lifetimes τ of the diffusing and reacting molecules are known:

$$\delta_R \approx (D\tau)^{1/2} \qquad (6)$$

[*] A stirrer in the electrolyzer and/or the recirculation of the electrolyte solution causes a "forced" convection; density differences in the electrolyte in the region of the electrode or rising gas bubbles cause "free" convection.

[**] The thickness δ_w is determined by the width of the layer, within which the velocity of the electrolyte decreases continuously towards zero.

[*] If δ_R according to Eq. (6) is less than $1/3\delta_N$, then the first (convection) term in Eq. (5) can be ignored.

If the species under consideration reacts according to a first order rate law with a rate constant k, then $\tau = 1/k$; for a second order reaction $\tau = 1/k c_{max}$ where c_{max} = the maximum concentration in the concentration profile. The thickness of the reaction layer for first and second order reactions can thus be estimated [Eq. (6a) or (6b)]:

$$\delta_R(\text{R.O.1}) \approx (D/k)^{1/2} \quad (6a)$$

$$\delta_R(\text{R.O.2}) \approx (D/k c_{max})^{1/2} \quad (6b)$$

c_{max} = maximal concentration of the reactive species in the concentration profile

For a rate constant k of $10^{-1}\ s^{-1}$, δ_R is 10^{-2} cm and decreases to about 10^{-7} cm when k is increased to $10^{9}\ s^{-1}$.

For $\delta_R < 10^{-7}$ cm it is unrealistic to talk in terms of a "reaction layer thickness", since this is defined just in terms of the kinetics of homogeneous reactions[*]. As the distance from the electrode surface approaches molecular dimensions such reactions ought to be viewed in terms of heterogeneous kinetics (see Section 2.4).

2.2. The Reaction of Long-Living Primary Species in the Bulk Electrolyte

Figure 4 depicts schematically the concentration profiles of two competing reactants, X and Y, which are dissolved in the electrolyte and which are assumed to react with the species formed in the first charge-transfer step. Figure 4a depicts the situation which holds for very long-living, *i.e.* very unreactive radical ions or radicals, whose lifetimes are greater than 10^{-1} s[*]. In such cases most of the intermediates, produced at the electrode, succeed in diffusing away from the electrode into the bulk of the solution, where they react under normal conditions *i.e.* with spatially constant concentrations of the reactants. The "place" of reaction, in this case, is the bulk of the electrolyte. The course of the reaction can then only be influenced (directed) by altering the concentrations of the competing reactants in the electrolyte itself.

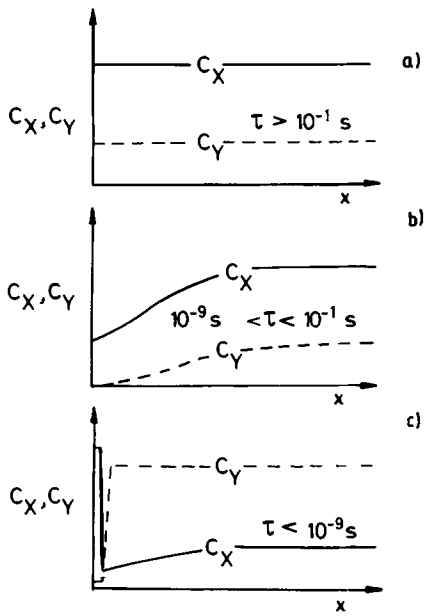

Fig. 4. The dependence of the concentration distribution of reactants X and Y in the reaction or in the diffusion layer on the lifetime τ of the primary species. a) The primary species reacts in bulk solution; the concentration ratio of the reactants X and Y are the same everywhere ($\tau > 10^{-1}$s). b) The primary species reacts homogeneously but close to the electrode surface (10^{-9}s $< \tau < 10^{-1}$s); Y is more reactive than X and the reaction layer is depleted of Y by restricted mass transport. c) Because of their short life-times ($\tau < 10^{-9}$s) or for other reasons (strong adsorption) the primary species reacts heterogeneously. Preferential adsorption can cause the relative concentrations of X and Y to be significantly different from those in the bulk solution. X is therefore favored over Y for heterogeneous reaction.

[*] This is justified, above all, because the composition of the electrolyte in the immediate neighborhood of the electrode is often different from that in the bulk of the solution. This is concerned with adsorption effects and the formation of the electrochemical double layer [10].

2.3. The Reaction of Short-Living Primary Species in the Reaction Layer

2.3.1. Mass Transfer Hindrance as a Method for Influencing the Concentrations of the Competing Reactants

If the lifetime of the primary product of charge transfer is less than 10^{-2} s then, under the usual mass-transfer conditions ($k_m = 10^{-3}$ to 10^{-2} cm/s) for electrolysis, the reaction layer will be thinner than the Nernst diffusion layer ($\delta_R < \delta_N$). Whenever the transport of any reactant, consumed in the vicinity of the electrode, is hindered, its concentration in the reaction layer can fall below that in the bulk of the solution. In an extreme case the concentration of the reactant in the reaction layer even falls to zero (Fig. 4b).

If, for example, the intermediate reacts much faster with Y than with X ($k_Y \gg k_X$) and transport of Y at the place of reaction is therefore hindered, then the reactant Y will be consumed very fast in the reaction layer and the slower reaction between the intermediate and X can successfully compete and under steady state conditions may become the predominant one[**]:

Then, in the reaction layer the following equation holds:

$$k_X \bar{c}_X \gg k_Y \bar{c}_Y \quad (7)$$

where $\bar{c}_X$ and $\bar{c}_Y$ = mean concentrations in the reaction layer

2.3.2. The Influence of the Current-Density on the Concentrations of the Reactive Species

To influence the concentration of the radicals or radical ions, respectively, by varying the current density (i[A/cm^2]) is another very important means for directing reactions. By

[*] In acetonitrile, dimethylformamide, and tetrahydrofuran, which are commonly used as solvents in electrochemical syntheses and which possess neither strongly nucleophilic nor electrophilic properties, such long lifetimes for the intermediates can always be expected if the anodic or cathodic half-wave potential of the depolarizer does not exceed +1 V (anodically) to −0.8 V (cathodically) (versus the aqueous saturated calomel electrode) [11, 42] and the "self-reaction", *i.e.* the radical recombination, for example, is especially slow. This is the case with the radical cation of bis(4-methoxyphenyl) sulfide, for example (see Section 3.1) [43].

[**] In the case of complete mass transfer hindrance of the more reactive reactant, which has a relatively low concentration in the bulk electrolyte, its reaction rate in the reaction layer depends only upon its mass transfer velocity $dN_x/dt = k_m c_x^{\infty}$ towards the electrode. *Fleischmann et al.* described a similar case in 1970 for the anodic oxidation of cyclohexane in the presence of chloride ions [13].

this method, which is typical for electrochemical processes, the rate of production of the reactive intermediate per unit area of surface can be altered almost at will[*]. Thus, it is possible to build up high steady-state concentrations of radicals or radical ions. By this means reactions of higher orders, *e.g.*, radical dimerizations or second order disproportionation reactions are favored over first (or pseudo-first) order reactions. Conversely, reactions of lower order are favored by decreasing the current-density.

In Table 1 the steady-state radical concentrations of anodically generated N_3 radicals (Eq. 8) at the anode ($x=0$) are listed for current-densities between 1 mA/cm^2 and 1 A/cm^2 [Eq. (8a)].

$$N_3^{\odot} - e \longrightarrow N_3^{\odot} \tag{8a}$$

For this calculation homogeneous kinetics and diffusion controlled dimerization of the N_3-radicals [Eq. (8b)][7] are assumed.

$$2\,N_3^{\odot} \xrightarrow{k_d} N_6 \longrightarrow 3\,N_2 \tag{8b}$$

The data in Table 1a were obtained by solution of Eq. (5), neglecting the convection term[7-9, 12].

$$D\left(\frac{\partial^2 c(N_3^{\odot})}{\partial x^2}\right) = k_d c^2(N_3^{\odot}) \tag{9a}$$

with the solution[7-9, 12]

$$c(N_3^{\odot})(x=0) = 1.14\,(i/F)^{2/3}\,(k_d D)^{-1/3} \tag{9b}$$

Table 1b lists the results of a second model calculation based on the assumption that the N_3-radicals react according to a pseudo-first order rate law, for example, by addition to an olefin, available in excess.

In this case the pseudo-first order reaction constant is obtained from Eq. (10).

$$k_{add}^{mono} = k_{add}\,c(\text{olefin})\ [s^{-1}] \tag{10}$$

The values in Table 1b were calculated by means of the differential equation

$$D\left(\frac{\partial^2 c(N_3^{\odot})}{\partial x^2}\right) = k_{add}^{mono}\,c(N_3^{\odot}) \tag{11a}$$

with the solution

$$c(N_3^{\odot})(x=0) = (i/F)\,(k_{add}^{mono} D)^{-1/2}\ [7\text{-}9] \tag{11b}$$

A value of 10^7 s^{-1} was assumed for k_{add}^{mono}[7] (cf. Table 4).

Table 1 shows that even for diffusion-controlled (and hence the fastest possible) bimolecular reaction of the reactive primary radicals and with the moderate current-density of 0.1 A/cm^2 a steady-state radical concentration of about 10^{-4} mol/L can be produced in the immediate neighborhood of the anode.

Table 1. Thickness of the reaction layer (δ_R) and the calculated concentration $c(N_3^{\odot})_0$ of anodically produced N_3-radicals at the electrode surface, where the N_3-radicals
a) undergo diffusion controlled recombination ($k_d \approx 10^{10}$ L mol^{-1} s^{-1})
b) react with styrene, (1 mol/L), according to a pseudo-first order rate law ($k_{add} = 10^7$ L mol^{-1} s^{-1})

a) Diffusion controlled recombination				
i [A/cm^2]	0.001	0.01	0.1	1
$c(N_3^{\odot})_0$ [mol/L]	1.15×10^{-5}	5.31×10^{-5}	2.47×10^{-4}	1.15×10^{-3}
δ_R [cm]	9.00×10^{-6}	4.34×10^{-6}	2.02×10^{-6}	9.30×10^{-7}
b) Addition to styrene				
$c(N_3^{\odot})_0$ [mol/L]	10^{-6}	10^{-5}	10^{-4}	10^{-3}
δ_R [cm]	1.04×10^{-6}	1.04×10^{-6}	1.04×10^{-6}	1.04×10^{-6}

From the ratio of the competing reactions [Eq. (12)]

$$\left\{\frac{r(\text{dimerization})}{r(\text{addition})}\right\}_{x=0} = \frac{k_d c(N_3^{\odot})_{x=0}^2}{k_{add} c(N_3^{\odot})_{x=0} c(\text{olefin})} \tag{12}$$

it can be shown that, at a current-density of 1 mA/cm^2, the pseudo-first order scavenger reaction is doubtlessly predominant, whereas at 1 A/cm^2 the bimolecular recombination reaction and the scavenger reaction proceed at nearly equal rates. In this case both the current density and the concentration of the olefin scavenger (which has a direct influence on the rate of addition) are very effective process variables for controlling the competition between radical addition and radical annihilation.

2.4. Heterogeneous Reactions of Short-Living Species on the Electrode Surface

If the lifetime of the reactive species is less than 10^{-9} s[*], the situation described above (homogeneous kinetics in the region in front of the electrode) is drastically altered: The reactive species no longer have sufficient time to escape from the electrode, the site of their generation. Heterogeneous kinetics can also be favored if the reactive species are strongly adsorbed at the electrode surface.

In these cases the reaction volume shrinks to the electrode/electrolyte interface. Reaction then takes place in a region where the chemical composition of the electrolyte differs, in some cases even to a high extent, from that in the bulk of the solution. In the case of strong adsorption (more precisely electrosorption[**]) of some compounds of the electrolyte the ratio of their surface concentrations (Γ_i) may differ markedly from the ratio of their bulk concentrations[14-16].

Figure 4c demonstrates schematically the effect of the preferential electrosorption of reactant X on the relative concentration of X and Y at the surface. These relative concentrations can often differ by several orders of magni-

[*] The upper limit of the current-density depends on the mass transfer velocity of the depolarizer to the electrode. The diffusion-limited current-density is given by $i_d = nFk_m c^{\infty}$. There is also a practical limit for the lowest applicable current-density, which depends upon the required minimal production rate of the electrolysis apparatus. For technical electrolyzers this limit is about 10 mA/cm^2.

[*] This holds for addition reactions of radicals to radical scavengers if the scavenger concentration amounts to 1 mol/L and a rate constant of more than 10^9 L mol^{-1} s^{-1} (that is nearly diffusion-controlled) reduces their lifetime to below this limit.

[**] The adsorption occurring at the electrode/electrolyte interface is called electrosorption because the adsorption equilibria are significantly affected by the electrode potential.

tude from those obtained in the electrolyte (see Fig. 5 and Fig. 6).

Eqs. (13a) and (13b) formally describe the consequences of this drastic alteration in the concentration ratio at the electrode/electrolyte interface for the selectivity of the heterogeneous reaction (assuming two possible parallel reactions).

$$\Gamma_X/\Gamma_Y \gg c_X^\infty/c_Y^\infty \tag{13a}$$

$$k_X^{het}\Gamma_X/k_Y^{het}\Gamma_Y \gg k_X^{hom}c_X/k_Y^{hom}c_X \tag{13b}$$

$$\text{when: } k_X^{het}/k_Y^{het} \approx k_X^{hom}/k_Y^{hom}$$

It must be mentioned that electrosorption equilibria—in general, adsorption equilibria at the electrode/electrolyte interfaces—are determined to the same extent by the nature of the electrode surface and by the chemical properties of the major components of the electrolyte (the liquid phase in general). Adsorption from liquid phases onto solid surfaces is, of course, always a displacement adsorption [Eq. (14a)]. Solvent molecules, L_{ads}, which were initially adsorbed at the solid surface must be displaced by the dissolved component X_{diss}:

$$\text{surface}\ldots L_{ads} + X_{diss} \rightleftharpoons \text{surface}\ldots X_{ads} + L_{diss} \tag{14a}$$

$$\Gamma_X = \Gamma_{max}\frac{K(X)_{ads}c(X)}{1+K(X)_{ads}c(X)} \tag{14b}$$

$$-RT\ln K(X)_{ads} = G^0(X_{ads}) + G^0(L_{diss}) - G^0(L_{ads}) - G^0(X_{diss}) \tag{14c}$$

Equations (14b) and (14c) describe the adsorption equilibrium in terms of the Langmuir isotherm and do not yet include the dependence of adsorption equilibria on electrode potential, with an arbitrarily variable potential. This dependence on potential is schematically reproduced in Figure 5 for neutral molecules S^0, anions $An^\ominus$ and cations

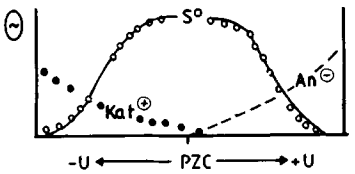

Fig. 5. Schematic presentation of the dependence of the electrosorption of cations ($Cat^\oplus$), anions ($An^\ominus$) and neutral molecules (S°) on the potential: Neutral molecules are most strongly adsorbed in the region of the potential of zero charge (PZC). If the electrode potential U differs sufficiently far from the point of zero charge (PZC ± 300 mV), then neutral molecules are desorbed. Cations are more strongly adsorbed at increasingly negative potentials, anions at increasingly positive potentials.

$Cat^\oplus$, whereby the importance of the potential of zero charge (E_{pzc}) point is to be emphasized. At this point the coulombic interaction between the dipolar solvent molecules normally used in electrolysis, and the electrode is at a minimum. For this reason the displacement of the solvent molecules by electrically neutral surface-active molecules is easiest at the potential of zero charge (E_{pzc}).

The coulombic interaction between the surface charge of the electrode and the solvent dipoles increases with increasing negative and more positive potentials that, ultimately, the adsorbed molecule can be desorbed again, *i.e.* completely displaced by the (usually relatively small) polar solvent molecules. For the same reason cations (anions) are adsorbed, above all, at potentials which are more negative (positive) than the PZC[17].

Figure 6 illustrates the dependence of the surface concentration of protonated strychnine adsorbed at the mercury/aqueous electrolyte interface on the electrode potential[18].

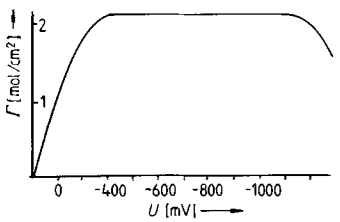

Fig. 6. Strychnine adsorption isotherm on mercury (pH 4.5, $c = 10^{-3}$ mol/L). The surface concentration Γ is plotted against the electrode potential (point of zero charge -400 mV *vs.* saturated calomel electrode (SCE)). At potentials more negative than -400 mV the mercury surface becomes saturated $\Gamma_s = 2.2 \times 10^{-10}$ mol/cm^2.

The importance of the nature of the solid surface can be demonstrated from an older example[19]: ethanol is adsorbed preferentially at polar surfaces (Al_2O_3, SiO_2) from an ethanol/benzene mixture, whereas the benzene is preferentially adsorbed at graphite. The following result makes the importance of the solvent evident: in order to saturate the mercury surface with strychnine, the strychnine concentration in 50/50 v/v aqueous ethanol must be about a hundred times higher than it need be in water alone[20].

Hence it is to be expected that the choice of a suitable electrode material and solvent/electrolyte system will enable deliberate establishment of whether the reactions, following the initial charge transfer, take place under homogeneous or heterogeneous kinetics[*].

The preferential adsorption of the primary species at the electrode surface can often lead to accelerated reaction of these species by heterogeneous catalysis[21] (cf. Section 4.1).

In the following sections the mechanistic and kinetic analysis of four electrosyntheses will be used to illustrate which of the different process variables or methods of controlling the reactant concentrations can be used, depending upon the reactivity and lifetime of the primary species, in order to improve the selectivity of a particular electrosynthesis. Table 2 summarizes the selected examples, which, with the exception of the first, refer to the physicochemical analysis of preparative investigations carried out by other authors.

The first example concerns relatively long-living radical cations, which are formed by the anodic oxidation of diaryl sulfides, and whose consecutive reactions can be very effectively influenced by altering the mass transport conditions[25].

The second case deals with the anodic oxidation of azide ions to N_3-radicals and their addition to olefins. The

[*] A good example of this is the Kolbe synthesis [23], which only takes place without side-reactions at the platinium electrode, while at the graphite anode the Hofer-Moest reaction takes place. The formation of "dimeric" 1,4-diazide compounds, during the oxidation of azide ions in the presence of olefins, at platinum anodes (but scarcely at graphite anodes), is closely related to the Kolbe synthesis [7].

Table 2. Four examples of improved selectivity in electrochemical synthesis.

Synthesis	Form of the first consecutive reaction	Means of improving the selectivity	Ref.
Anodic synthesis of triarylsulfonium ions	Homogeneous-kinetic	a) Altering the reactant concentration in the bulk of the solution b) Inhibition of mass transfer	[41-44]
Anodic additon of N_3-radicals to olefins forming monomeric 1,2- and dimeric 1,4-diazides	Homogeneous-kinetic	a) Choice of anode material (Pt) b) Increasing the olefin concentration c) Lowering the current-density	[7, 46, 47]
Cathodic reduction of 2-acetylpyridine to 1-(2-pyridyl)ethanol with asymetric induction	Heterogeneous-kinetic	a) Electrosorption of the inductor b) Choice of cathode material (Hg, Pb)	[50-55, 57, 58]
Anodic oxidation of vinyl compounds to 1,2- and 1,4-diol ethers	Heterogeneous-kinetic	a) Choice of anode material b) Control of mass-transport	[11, 27-29, 61, 62]

N_3-radicals react according to homogeneous kinetics at platinum anodes[7, 26]. At carbon anodes, however, their reaction is mainly heterogeneous.

The third example derives from the cathodic reduction of 2-acetylpyridine, which leads to pinacols by heterogeneously catalyzed dimerization at the mercury cathode; however, covering the electrode surface with suitable, optically active proton donors enables the synthesis of optically active 1-(2-pyridyl)ethanol[24, 54][*].

The last example deals with the anodic oxidation of olefins—especially of styrene. In this case the heterogeneous kinetics of the consecutive reaction of the primarily formed intermediate make it possible to use either control of mass transport or choice of the anode material to steer the reaction so that either only "monomers" or mainly "dimers" are formed (monomer and dimer refer only to the carbon skeleton)[11, 27-29][**]. In this context it should be mentioned that *Savéant*'s group[30-33] has recently studied the detailed course of the reaction and the selectivity of the overall reaction in the cathodic reduction of aryl halides in organic solvents. *Savéant*'s results, in as far as they deal with comparable cases, confirm the ideas presented here.

3. Improving the Selectivity of Consecutive Reactions having Homogeneous Kinetics

3.1. Triarylsulfonium Ions by Anodic Oxidation of Diaryl Sulfides in Non-Aqueous Solution

The anodic oxidation of diaryl sulfides in aqueous solution leads to the formation of diaryl sulfoxides[38] [Eq. (15)]:

$$R^1\text{—}S\text{—}R^2 + H_2O - 2e \rightarrow R^1\text{—}SO\text{—}R^2 + 2H^{\oplus} \quad (15)$$

R^1, R^2 = alkyl, aryl

In non-aqueous solvents of low basicity (*e.g.* in acetonitrile) and in the presence of an arene, triarylsulfonium ions are formed [Eq. (16)][*]. In this case an anodic SC-coupling reaction takes place instead of an SO-coupling[41] [Eq. (16)]:

$$R^1\text{—}S\text{—}R^2 + HR^3 - 2e \rightarrow R^1R^2R^3S^{\oplus} + H^{\oplus} \quad (16)$$

R^1, R^2, R^3 = aryl

This anodic SC-coupling is, however, non-selective, because the diaryl sulfide competes with the added arene. In the few cases investigated so far this leads to the almost exclusive formation of the unwanted self-coupling product [Eq. (17)]:

$$2R^1\text{—}S\text{—}R^2 - 2e \rightarrow R^1R^2S^{\oplus}\text{—}R\text{—}S\text{—}R^2 + H^{\oplus} \quad (17)$$

R = R^1 minus H

Magno and *Bontempelli* found only the self-coupling product when diphenyl sulfide was oxidized in the presence of benzene or ditolyl sulfide in the presence of toluene[41].

The anodic oxidation of bis(methoxyphenyl) sulfide in the presence of anisole, gives, in contrast, a very good yield of tris(methoxyphenyl)sulfonium ions[42]. The only by-product is bis(methoxyphenyl) sulfoxide, formed from the primary radical cation and the last few traces of water remaining in the solvent (anhydrous acetonitrile).

3.1.1. The Chemical Reaction of the Radical Cations of Various Diaryl Sulfides

Relatively stable radical cations of diaryl sulfides are generated in the first charge transfer step at potentials of between 1 and 1.5 V (*vs.* SCE) according to Eq. (18)[42, 43].

$$R^1\text{—}S\text{—}R^2 - e \rightleftharpoons (R^1\text{—}S\text{—}R^2)^{\odot\oplus} \quad (18)$$

The S-radical cations do not react directly with nucleophiles, such as arenes, water or unreacted diaryl sulfide.

The dication, however, which is constantly supplied by the fast disproportionation equilibrium [Eq. (19)], reacts with nucleophiles; after deprotonation the stable end-product P_i is formed [Eq. (20)][43, 44].

[*] Ketyl radicals, generated by cathodic reduction of 2- and 4-acetylpyridines, dimerize to pinacols in a heterogeneously catalyzed reaction at the mercury cathode. Their adsorption can be inhibited by competitive adsorbants, thus checking the formation of pinacols [24].

[**] The industrial interest in the anodic C—C bond formation reactions of the second and fourth examples is obvious. The first reaction allows use of triarylsulfonium salts as electrolytically regenerable arylation reagents (*e.g.* in the arylation of amines) [34—37]. The third reaction could point the way to easily performed, induced asymmetric synthesis, requiring only catalytic amounts of the inductor.

[*] For arylation using triarylsulfonium salts see [34—37]. However, triarylsulfonium salts can be easily synthesized by non-electrochemical methods (or reactions) like the Friedel-Crafts reaction between diaryl sulfides and aryl halides [39] or the reaction of diaryl sulfides and diaryliodonium salts [40].

$$2(R^1\text{—}S\text{—}R^2)^{\oplus\ominus} \rightleftharpoons (R^1\text{--}S\text{—}R^2)^{2\oplus} + R^1\text{—}S\text{—}R^2 \quad (19)$$

$$(R^1\text{—}S\text{—}R^2)^{2\oplus} + Nu_i \xrightarrow{k_i} (R^1\text{—}S(Nu_i)\text{—}R^2)^{2\oplus} \xrightarrow{-H^{\oplus}} P_i \quad (20)$$

The reaction sequence (18) to (20) is described by the following rate law [(Eq. (21)]:

$$r(P_i) = k_i K_{dis} c^2(\text{rad.-cat}) \times c(Nu_i)/c(\text{diaryl sulfide}) \quad (21)$$

K_{dis} = disproportionation constant

Table 3 summarizes the redox potentials[*] of the charge transfer equilibrium [Eq. (18)] for several diaryl sulfides, as well as the apparent rate constants $k_i^{form} = k_i K_{dis}$ [L mol^{-1} s^{-1}] for coupling reactions between primarily formed radical cations and nucleophiles (as far as they are known). There is a good correlation between the formal rate constants of the consecutive reactions and the redox potentials of the sulfides[**]. The rate is influenced by the nucleophilicity of the coupling partner, just as is expected for electrophilic substitution reactions [Eq. (20)].

Table. 3. Redox potentials E_0 (*vs.* SCE) of the redox pair diaryl sulfide/diaryl sulfide radical cation and apparent constants ($k_i^{app} = k_i K_{dis}$) for the coupling reaction of the radical cation to various partners (23 °C, 0.1 mol/L $NaClO_4$ in acetonitrile).

R in R_2S	E_0 [mV *vs.* SCE]	k_i^{app} [L mol^{-1} s^{-1}] for the reaction of $R_2S^{\oplus\ominus}$ with: H_2O	R_2S	Anisole	Mesitylene	RH
Phenyl	1483	10^7	6×10^7	—	5×10^5	10^4 (Benzene)
4-Tolyl	1380	10^6	5×10^6	—	5×10^6	3×10^4 (Toluene)
Mesityl	1340	—	[a]	—	100	100 (Mesitylene)
4-Methoxyphenyl	1080	80	[a]	240	40	240 (Anisole)

[a] No reaction; $k_i < 100$.

The composition of the product mixture [Eq. (22)] resulting from the simultaneous reaction of the primarily formed radical cation with several nucleophiles can be calculated from Eq. (21).

$$c(P_1)/c(P_2)/c(P_3) = k_1\bar{c}(Nu_1)/k_2\bar{c}(Nu_2)/k_3\bar{c}(Nu_3) \quad (22)$$

$\bar{c}(Nu_i)$ is the average concentration of nucleophile in the reaction layer (δ_R) [Eq. (23)]:

$$\bar{c}(Nu_i) = 1/\delta_R \int_{x=0}^{x=\delta_R} c(Nu_i)\,dx \quad (23)$$

3.1.2. Improving the Selectivity of the Anodic Synthesis of Triarylsulfonium Ions

The anodic synthesis of tris(4-methoxyphenyl)sulfonium ions in acetonitrile avoiding the formation of sulfoxide: the relatively stable radical cation from bis(4-methoxylphenyl) sulfide does not form the unwanted self-coupling product in acetonitrile if more than 10^{-1} mol/L anisole is present. However, even when very carefully dried acetonitrile is used as the solvent bis(4-methoxyphenyl) sulfoxide is formed, since the water content of the electrolyte cannot be reduced to less than about 0.1—0.2% w/w (*ca.* 10^{-1} mol/L). The selectivity of formation, η, of tris(4-methoxyphenyl)sulfonium ions [Eq. (24)] significantly depends upon the concentration ratio c(anisole)/$c(H_2O)$:

$$\eta = \frac{1}{1 + k(H_2O)\cdot c(H_2O)/k(\text{anisole})\cdot c(\text{anisole})} \quad (24)$$

Figure 7 indicates the experimentally determined selectivity for the formation of tris(4-methoxyphenyl)sulfonium ions under the given concentration ratios $c(H_2O)/c$(anisole) (broken line calculated from Eq. (24)). The yields obtained at low water concentrations are better than the calculated values, thus reflecting depletion of water in the diffusion and reaction layers. At current-densities of $i \geq 0.5 i_d$ the selectivity is improved by depletion of water (the more reactive nucleophile) in the diffusion and reaction layers (cf. Fig. 4b).

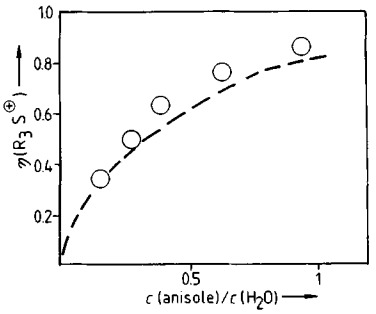

Fig. 7. Dependence of the selectivity (current yield) η for the anodic synthesis of tris(4-methoxyphenyl)sulfonium ions on the relative concentrations of anisole and water in the electrolyte (acetonitrile/$NaClO_4$). Broken line: calculated value according to Eq. (24).

Attempted preparation of tri-4-tolyl and triphenylsulfonium ions: Magno and *Bontempelli*[41] found only anodic self-coupling products in the anodic oxidation of diphenyl and di-4-tolyl sulfides. This is caused by the very different rate constants for the self-coupling and for coupling to benzene or toluene, respectively. In the system di-4-tolyl sulfide/toluene the self-coupling reaction is 100 times faster than the coupling with arene, in the system diphenyl sulfide/benzene more than 1000 times faster (Table 3).

Equation (25) represents the selectivity for the case where coupling to water as a nucleophile can be neglected:

$$\eta(R_3S^{\ominus}) = \frac{dc(R_3S^{\ominus})/dt}{dc(R_3S^{\oplus})/dt + dc(R_2S\text{—}R'SR^{\ominus})/dt} = \frac{k_1\bar{c}(RH)}{k_1\bar{c}(RH) + k_2\bar{c}(R_2S)} \quad (25)$$

$\bar{c}_i$ = mean concentration in the reaction layer
R′ = R minus H

It can be seen immediately from Eq. (25) that the reaction will be the more selective the smaller the concentration of diaryl sulfide and the higher the concentration of the arene in the reaction layer at the electrode.

[*] The redox potentials of the redox pair diaryl sulfide/diaryl sulfide radical cation can be obtained from the half-wave potential for the oxidation of diaryl sulfides, taking into account the chemical kinetics of the reaction.

[**] Higher redox potentials correspond to an increased reactivity of the radical ion; consequently increased rates of reaction are to be expected if a homologous compound has a higher redox potential.

If the current-density i of the working electrode approaches the diffusion-limited current-density i_d then the concentration of the depolarizer, *i.e.* of the diaryl sulfide, at the electrode decreases markedly compared to its concentration in bulk solution. By utilizing this effect it is possible to establish conditions in the reaction layer which are significantly more favorable for coupling with the arene (cf. Fig. 4b). To a good approximation Eq. (26) holds for the diaryl sulfide concentration in the reaction layer region[*]:

$$c_x(R_2S) \approx [1-(i/i_d)]\,c^\infty(R_2S) \qquad (26)$$

$x \leqslant \delta_R$; c^∞ = concentration in bulk solution
x = distance from the electrode

Accordingly, the dependence of the selectivity on the bulk concentration (c^∞) of the diaryl sulfide or the arene and on the current-density is given by Eqs. (25)—(27):

$$\eta(R_3S^\oplus) = \frac{a}{1+a-i/i_d} \qquad (27)$$

$$a = k_1/k_2(c^\infty(RH)/c^\infty(R_2S))$$

In Figure 8a the experimentally determined selectivities for the coupling of di-4-tolyl sulfide with toluene to form tri-4-tolylsulphonium ions are plotted as a function of i/i_d.

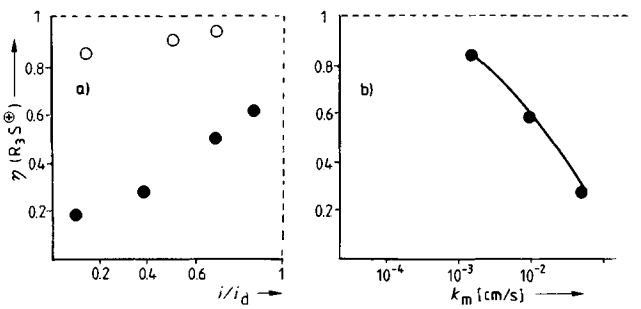

Fig. 8. Selectivity (current yield) η for the anodic synthesis of tri-4-tolylsulfonium ions. a) Dependence on the ratio of the actual current-density i and the diffusion-limited current-density i_d on using platinum (•) or graphite anodes (o). b) The dependence on mass transport coefficient k_m (at 70% i_d).

With platinum anodes, on approaching the diffusion-limited current ($i/i_d \rightarrow 1$) the yield of tri-4-tolylsulfonium, which is about 20% for very low current-densities with a toluene concentration of 1 mol/L and a di-4-tolyl sulfide concentration of 10^{-2} mol/L, can actually be raised to 60% (the full circles in Fig. 8a). Under practical electrolysis conditions it is not easy to adjust the current at the working electrode close to the diffusion-limited current. A somewhat smaller current-density is to be recommended together with a lowering of the concentration of the depolarizer, di-4-tolyl sulfide, within the reaction layer, by use of a mass transfer barrier[**]. The open circles show the results of the same electrosynthesis using carbon instead of platinum electrodes. In this case the kinetics of the reaction are no longer homogeneous but heterogeneous[*] and thus the selectivity is (fortunately) increased. It is not possible—even with carbon electrodes—to produce detectable quantities of triphenylsulfonium ions by the oxidation of diphenyl sulfide in the presence of benzene[43,44].

Fig. 8b shows the calculated and observed dependence of η on the mass transport coefficient k_m.

3.2. Addition of Anodically Produced Radicals to Olefins

3.2.1. Outline of the Reaction

It has been known for more than ten years[46] that radicals formed by the anodic oxidation of the corresponding anions add to olefins. "Dimeric" 1,4-disubstituted and "monomeric" 1,2-disubstituted hydrocarbons are formed [Eqs. (28)—(31)].

$$X^\ominus - e \rightleftharpoons X^\odot \qquad (28)$$

$$X^\odot + R^1R^2C{=}CR^3R^4 \rightarrow R^1R^2XC{-}\overset{\oplus}{C}R^3R^4 \qquad (29)$$

$$R^1R^2XC{-}\overset{\oplus}{C}R^3R^4 + X^\ominus \rightarrow R^1R^2XC{-}CXR^3R^4 \qquad (30)$$

$$2\,R^1R^2XC{-}\overset{\oplus}{C}R^3R^4 \rightarrow (R^1R^2XC{-}CR^3R^4)_2 \qquad (31)$$

Schäfer et al. have exhaustively studied the general applicability of such syntheses[47].

The structures and types of the electrolysis products are determined by the choice of the anode material. At platinum anodes good yields of the dimeric products are achieved [Eq. (31)], while significantly more monomeric disubstituted hydrocarbons are produced at carbon and graphite anodes [Eq. (30)]. The monomeric products formed at carbon anodes often contain different substituents X and Y, where Y is a nucleophilic group which often originates from the solvent molecule[**].

3.2.2. Anodic Addition of N_3-radicals to Olefins

The electrode kinetics of the oxidation of azide ions in non-aqueous solutions at various anodes: The electrode kinetics of the anodic oxidation of azide anions has been investigated at graphite, vitreous carbon, and platinum electrodes, both in the absence and in the presence of various olefins. This reaction provides a very suitable model for the reaction type described by Eqs. (28)—(31).

The technique used made it possible to investigate the kinetics of the chemical reactions of the primarily formed species and to clarify one of the main reasons for the electrolysis at graphite and at platinum electrodes proceeding so differently[7,26]. The study is based on the analysis of steady-state current-voltage curves, which were quantitatively evaluated in terms of the homogeneous kinetic model outlined in Section 2.3. Table 4 contains formal rate constants obtained for the dimerization of N_3-radicals and for the addition of these radicals to various olefins at the three electrode materials mentioned above.

[*] This approximation assumes that the thickness of the reaction layer δ_R is less than 10% of the thickness of the diffusion layer δ_N.

[**] Covering the electrode with either thin felt or cloth can provide a mass transfer barrier and the effective thickness of the diffusion layer is determined by its thickness, so that the diffusion-limited current-density and the space-time yield of the apparatus decrease as the reciprocal of the thickness of the material. In such cases special electrolytic cells, *e.g.* Swiss-roll cells [45], must be used.

[*] It can be shown by analysis of the current-voltage curves that the steady-state radical concentration at carbon anodes is reduced [44], so at the graphite surface the reaction of diaryl sulfide dications is presumably heterogeneously catalyzed.

[**] For electrolyses in alcohols ROH or in acetonitrile, Y = OR or (after hydrolysis) Y = NH—CO—CH_3.

Table 4. Apparent [a] rate constants k_{add} (calculated from the homogeneous-kinetic model) for the addition of anodically produced N_3-radicals to olefins using platinum, vitreous carbon, and graphite anodes (Sigri P 127) [7].

$N_3^{\odot}$ + reactant	k_{add} [L mol^{-1} s^{-1}] Platinum	Methyl radicals [b]	Vitreous carbon	Graphite
$N_3^{\odot}$ [c]	10^{10}	—	5×10^{11}	2×10^{13}
1-Octene	2×10^{5}	(2×10^{3})	3×10^{5}	1.1×10^{9}
cis-Stilbene	1×10^{6}	(4×10^{3})	7.5×10^{6}	8.4×10^{9}
trans-Stilbene	4×10^{7}	(1×10^{4})	4.8×10^{8}	2.1×10^{11}
Styrene	2×10^{7}	(1×10^{5})	1.5×10^{8}	7×10^{10}
1,1-Diphenylethylene	6×10^{7}	(2×10^{5})	6×10^{8}	2×10^{11}
1,4-Diphenylbutadiene	4×10^{8}	—	1.5×10^{10}	6.4×10^{12}

[a] Such values, when calculated from electrode-kinetic data, can be larger than would be expected for diffusion controlled processes ($\approx 10^{10}$ L mol^{-1} s^{-1}), if the reaction is heterogeneously catalyzed. [b] Comparison values for the homogeneously catalyzed reaction of methyl radicals [49a]. [c] Dimerization.

The apparent rate constant k_{add} of the reaction clearly depends on the electrode material. The $N_3^{\odot}$-dimerization, as well as the addition of $N_3^{\odot}$-radicals to olefins, is fastest at graphite, less fast at vitreous carbon, and slowest at platinum anodes.

In several cases at vitreous carbon and especially at graphite anodes the rate constants calculated from the experimentally measured N_3-radical concentrations at the anode are virtually higher than those expected for a diffusion-controlled reaction (10^{10} L mol^{-1} s^{-1}). These observations can only be explained by assuming that the reactions at vitreous carbon and, even more, at the graphite anodes, are heterogeneously catalyzed, while at the platinum anode they mainly follow homogeneous kinetics (*i.e.* in the solution). This is the reason why the apparent rate constants, calculated using a homogeneous kinetic model, are higher than for diffusion-controlled reactions.

For comparison with the rate constants for homogeneous kinetic addition determined at platinum anodes, Table 4 also shows the rate constants for the addition of methyl radicals to olefins[49a]. As a result of the higher reactivity of $N_3^{\odot}$ k_{add} for $N_3^{\odot}$ is, of course, two or three orders of magnitude greater than for $CH_3^{\odot}$, the rate constants, however, are similarly graduated according to the type of the olefin. $N_3^{\odot}$ seems to be more electrophilic than $CH_3^{\odot}$, as shown by the distinctly higher values of the rate constant obtained for addition to phenyl-substituted vinyl compounds.

The different reaction mechanism of N_3-radicals at platinum and graphite electrodes, *i.e.* homogeneous *vs.* heterogeneous kinetics, also explains the different results obtained in preparative electrochemical syntheses at these electrodes[26].

At the platinum electrode the oxidation of azide ions in the presence of styrene can give good yields of 1,4-diazido-2,3-diphenylethane together with only a small amount of 1,2-diazido-1-phenylethane (cf. Fig. 9a):

$$2\,N_3^{\odot} - 2e + 2\,C_6H_5CH{=}CH_2 \rightarrow (N_3CH_2{-}C(C_6H_5)H)_2 \qquad (32a)$$

At the carbon electrode, however, the fraction of this dimeric product is much lower and the monomeric 1,2-diazido-1-phenylethane is the major product.

$$2\,N_3^{\odot} - 2e + C_6H_5CH{=}CH_2 \rightarrow C_6H_5CHN_3{-}CH_2N_3 \qquad (32b)$$

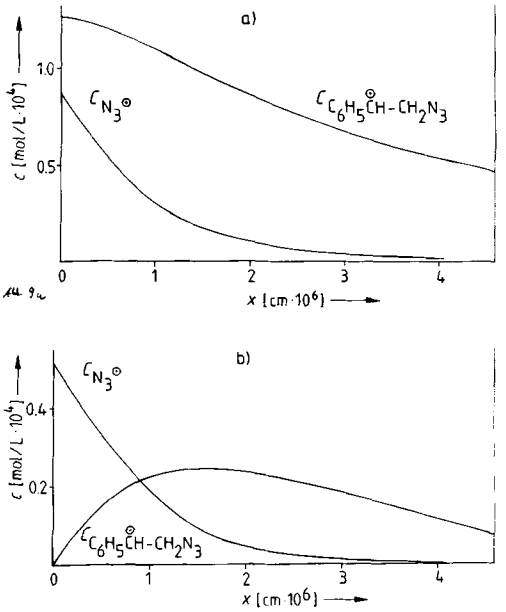

Fig. 9. Calculated concentration profiles for N_3-radicals and secondary *C*-radicals for the anodic oxidation of azide ions in the presence of styrene. The calculation was based on the electro-kinetically measured rate constant for the addition of N_3-radicals to styrene ($k_{add} = 10^7$ L mol^{-1} s^{-1}). The relative current yields η_{rel} given below were calculated from the profiles, and agree satisfactorily with the results obtained experimentally for Fig. 9a (Pt) and to a less extent for Fig. 9b (*C*). $i = 100$ mA/cm^2, $k_{add} \cdot c(\text{styrene}) = 10^7$ s^{-1}. a) Oxidation at the platinum anode, b) oxidation at the carbon anode. In contrast to case (a) it is assumed that the oxidation of the *C*-radical to carbonium ion is not hindered at the carbon electrode.

η [%]	Pt-Anode Calc.	Pt-Anode Obs.	C-Anode Calc.	C-Anode Obs.
Dimer	75.5	70	5.7	10
Monomer	17.4	20	91.6	40
N_2	7.1	10	2.7	50

The reason would appear to be that at platinum anodes a further oxidation of the *C*-radicals formed [Eq. (29)] is inhibited[49b].

$$R^1R^2XC{-}\overset{\odot}{C}R^3R^4 - e \rightarrow R^1R^2XC{-}\overset{\oplus}{C}R^3R^4 \qquad (32c)$$

This results in the preferred dimerization reaction of the *C*-radical [Eq. (31)] produced according to Eq. (29), together with the competitive reaction of the *C*-radical with N_3-radicals to form the monomer [Eq. (30)].

Figure 9a delineates the calculated concentration profiles of N_3- and *C*-radicals at the platinum electrode. The calculations are based on the rate constants of the addition reactions, obtained from the electrode kinetic measurement. The yields, which correspond to the calculated profiles, are in good agreement with those obtained preparatively.

At the carbon anode the addition [Eq. (29)] takes place, to a large extent, according to heterogeneous kinetics and, moreover, further oxidation of the homogeneously produced *C*-radicals to carbonium ions seems to be only slightly inhibited. Figure 9b shows the concentration profiles expected under these conditions for N_3- and *C*-radicals, together with the calculated current yields. Although the agreement between experimental yields and those calculated from kinetic data is worse than in Figure 9a, Figure 9b illustrates the important point: a remarkable in-

crease in the yield of monomer compared to the dimer[*]. When a carbon electrode is used the end-products of anodic addition of N_3-radicals to olefins are mainly monomers. They very likely result from the reaction of the carbocations, produced according to Eq. (32c), with nucleophiles (azide ions, basic solvent, anions of the conducting electrolyte and, in rate instances, unreacted olefin). Three of the possible terminal reactions for the addition of N_3 radicals to styrene at the carbon electrode[26] are presented in Eqs. (33)–(35).

$$C_6H_5\overset{\oplus}{C}H—CH_2N_3 + N_3^{\ominus} \rightarrow C_6H_5CHN_3—CH_2N_3 \quad (33)$$

$$C_6H_5\overset{\oplus}{C}H—CH_2N_3 + Nu^{\ominus} \rightarrow C_6H_5CHNu—CH_2N_3 \quad (34)$$

$$C_6H_5\overset{\oplus}{C}H—CH_2N_3 + CH_3—CN \rightarrow C_6H_5—CH(\overset{\oplus}{N}C—CH_3)—CH_2N_3$$
$$\xrightarrow{\text{solvolysis}} C_6H_5—CH(NH—CO—CH_3)—CH_2N_3 \quad (35)$$

Optimization of the anodic addition of N_3-radicals to styrene, using the platinum electrode: In this case two problems need to be solved:

1) How can the unwanted destruction of the anodically produced N_3-radicals by dimerization [Eq. (8b)] be avoided?
2) How can the highest yield of dimer [Eq. (32a)] be achieved?

Radical dimerization is a second order reaction with respect to N_3-radicals. On the other hand, the addition reaction according to Eq. (29) is first order with respect to N_3-radicals. The annihilation of N_3-radicals can, therefore, be checked by reducing the current-density, and increasing the olefin concentration, if Eq. (36) applies:

$$k_{add}c(\text{styrene}) > k_{dim}c(N_3^{\odot})_{x=0} \quad (36)$$

In order to optimize the yield of dimer it must be taken into account that reactions (30) [≙(38)] and (31) [≙(37)] compete with each other in the reaction layer and that both reactions have diffusion-controlled rates ($k_d \approx 10^{10}$ L mol^{-1} s^{-1}):

$$2\,C_6H_5\overset{\odot}{C}H—CH_2N_3 \xrightarrow{k_d} (N_3CH_2—C(C_6H_5)H)_2 \quad (37)$$

$$C_6H_5\overset{\odot}{C}H—CH_2N_3 + N_3^{\odot} \xrightarrow{k_d} C_6H_5CHN_3—CH_2N_3 \quad (38)$$

The yield of dimer can be increased by raising the olefin concentration, which accelerates the addition [Eq. (29)] and reduces the steady-state concentration of N_3-radicals in the reaction layer, as well as by reducing the anodic current-density i, which has the same effect. Eq. (39) reproduces this correlation formally:

$$\frac{\bar{r}(\text{dimer formation})}{\bar{r}(\text{monomer formation})} \sim (c(\text{olefin})/i)^{1/2} \quad (39)$$

$\bar{r}$ = the reaction velocity averaged over the reaction layer

Eq. (39) holds only approximately and only for the range $0.3 < (1-\eta(N_2)) < 0.7$. Figure 10 shows the dependence of the yields for monomer, dimer, and unwanted nitrogen production on the current-density and on the styrene concentration; Eq. (39) is thus semi-quantitatively verified.

[*] The heterogeneously catalyzed acceleration of the dimerization of $N_3^{\odot}$ at the carbon anode [cf. Eq. (8b)] is not included in the homogeneous kinetic model, used in calculating the data for Figure 9b.

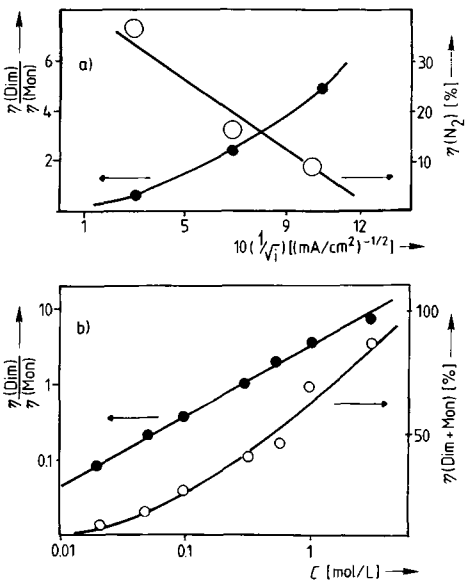

Fig. 10. Competing reactions during the anodic addition of N_3-radicals to styrene. a) Dependence of the ratio of dimer to monomer yield and the yield of N_2 (produced by the annihilation of $N_3^{\odot}$ by dimerization) upon the current-density i. Raising the current-density favors annihilation (c(styrene) = 1 mol/L). b) Dependence of the ratio of the dimer to monomer yield and the total yield on the styrene concentration c. Both the yield ratio and the total yield are improved by raising the styrene concentration (i = 46 mA/cm^2).

4. Improving the Selectivity of Consecutive Reactions having Heterogeneous Kinetics

4.1. The Cathodic Reduction of 2-Acetylpyridine

4.1.1. Asymmetrical Induction by Adsorbed, Optically-Active Species

The work of *Horner et al.*[50,51], *Grimshaw et al.*[52], *Jubault et al.*[53] and *Kariv et al.*[54] has demonstrated that the production of one of the two possible optical isomers can be favored in the cathodic reduction of carbonyl to hydroxyl compounds in the presence of surface-active, optically-active organic compounds. Asymmetrical induction has also been achieved by anodic processes in the presence of surface-active inductors[55]. The best optical yields were obtained by *Kariv et al.* for the reduction of 2-acetylpyridine to 1-(2-pyridyl)ethanol in the presence of protonated strychine at the mercury electrode. The optical yield was up to 50% (75% (+)isomer, 25% (−)isomer).

4.1.2. Polarographic Investigation and Preparative Course of Acetylpyridine Reduction in the Presence and Absence of Strychnine

The polarogram of 2-acetylpyridine in aqueous or aqueous/alcoholic solution at pH values between 0 and 3.5 exhibits two separate one-electron waves (Fig. 11a). The first wave has reversible characteristics and its half-wave potential is pH-dependent. The wave is steeper than would be expected for a "normal" one-electron wave[*].

[*] A normal reversible one-electron wave, as observed in the polarography of, *e.g.*, cobaltocenium ions, has a slope of (60 mV)$^{-1}$ per decade when $\lg[(i_d - i)/i]$ is plotted against U_i; its half-wave potential is pH-independent [56].

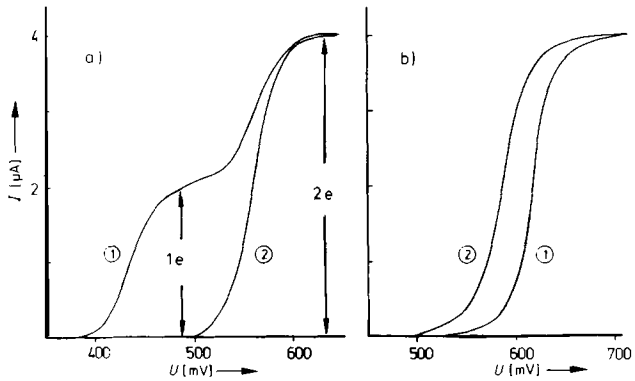

Fig. 11. Polarograms of the cathodic reduction of 2-acetylpyridine. a) pH 2. Curve 1: two separate one-electron waves, aqueous electrolyte without addition of a surface-active agent; Curve 2: one two-electron wave in the presence of 10^{-4} mol/L tetrabutylammonium ion. b) pH 4.4. Curve 1: one two-electron wave in the presence of 10^{-4} mol/L tetrabutylammonium ion; Curve 2: The half-wave potential is displaced to a more positive potential (U *vs.* SCE) when the tetrabutylammonium ion is replaced by the equally strongly adsorbed but strongly protonated strychnine.

A first order reaction with respect to proton concentration is indicated by the pH-dependence and, from the slope of the wave it can be deduced[57] that the ketyl, primarily produced at the cathode [Eq. (40)], is consumed in a heterogeneous second order reaction. It could be assumed that a pinacol is formed under these conditions by dimerization according to Eq. (41).

$$\text{Pyr—CO—CH}_3 + e + H^{\oplus} \rightleftharpoons \text{Pyr—}\overset{\odot}{\text{C}}\text{OH—CH}_3 \quad (40)$$

$$2\,\text{Pyr—}\overset{\odot}{\text{C}}\text{OH—CH}_3 \rightarrow (\text{Pyr—C(OH)(CH}_3))_2 \quad (41)$$

Pyr = 2-Pyridyl

On addition of surface-active but chemically inert substances such as tetrabutylammonium ions, which are strongly adsorbed at the mercury surface, only one reversible two-electron wave is observed instead of two one-electron waves (Fig. 11a). The pH-dependence of its half-wave potential indicates a reaction order of two concerning participation of protons.

On the basis of the electrode-kinetic data the two-electron wave can be assigned to the formation of 1-(2-pyridyl)ethanol, which proceeds according to Eqs. (42) and (43) *via* a preliminary, fast electrochemical/protolytic equilibrium (with the transfer of two electrons) followed by protonization [Eq. (44)] of the intermediate carbanion:

$$\text{Pyr—CO—CH}_3 + e + H^{\oplus} \rightleftharpoons \text{Pyr—}\overset{\odot}{\text{C}}\text{OH—CH}_3 \quad (42)$$

$$\text{Pyr—}\overset{\odot}{\text{C}}\text{OH—CH}_3 + e \rightleftharpoons \text{Pyr—}\overset{\ominus}{\text{C}}\text{OH—CH}_3 \quad (43)$$

$$\text{Pyr—}\overset{\ominus}{\text{C}}\text{OH—CH}_3 + HA \rightarrow \text{Pyr—CHOH—CH}_3 \quad (44)$$

The formation of dimers [Eqs. (40) and (41)] only takes place at the free, unoccupied mercury surface, *i.e.* reaction (41) is a surface reaction in which adsorbed ketyls react with each other. Thus, the dimerization is heterogeneously catalyzed.

If the adsorption of the ketyls is prohibited by competitive adsorption at the mercury surface, then the homogeneous kinetic dimerization[*] is significantly slower than the subsequent reduction [Eq. (43)] and the final homogeneous kinetic protonization [Eq. (44)] to an alcohol. If the inert surface-active tetrabutylammonium ion is replaced by a surface-active, *i.e.* strongly adsorbed, proton donor, *e.g.* protonated strychnine, then this reaction can be greatly accelerated by heterogeneous catalysis. Figure 11b illustrates this effect in the displacement of the half-wave potential of the two-electron reduction of 2-acetylpyridine to more positive potentials (cf. Fig. 6 for the adsorption of strychnine). The displacement corresponds to a 20-fold reduction in the concentration of the reduced partner, as a result of accelerated protonation, in the cathodically produced redox system, that determines the potential. The simplest explanation for this effect is that the homogeneous reaction-steps (42), (43), and (45) become heterogeneous due to participation of adsorbed strychnine, whose local concentration—due to adsorption—is significantly increased.

$$\text{Pyr—}\overset{\odot}{\text{C}}\text{OH—CH}_3 + {}^{\oplus}\text{H—Strych}_{ads} \rightarrow \text{Pyr—}\overset{\star}{\text{C}}\text{HOH—CH}_3 + \text{Strych}_{ads} \quad (45)$$

Figure 6 shows the adsorption isotherm for strychnine at pH 4.5. If the strychnine concentration is 10^{-3} mol/L then the electrode surface is completely covered with strychnine over a wide range of potentials, *i.e.* the condition is fulfilled for the maximum rate of reaction (45).

The adsorbed strychnine does not only act as proton donor for the preestablished equilibrium (42) and the very fast, final reaction (45) but, at the same time, provides the chiral matrix, which leads to the asymmetrical induction. All the conclusions drawn from the electrode-kinetic evidence have been confirmed in preparative electrolysis[57].

The problem of increasing the selectivity of the heterogeneous kinetically-controlled, asymmetrical synthesis has many facets:

Firstly, an inductor must be found that has not only a structure[*] but also an acidity that is optimal for asymmetrical induction.

Furthermore, the pH of the electrolyte must, on the one hand, be high enough to ensure that the protonation, which proceeds homogeneously [Eqs. (42), (43), and (44)], is slower than that proceeding heterogeneously [Eqs. (42), (43), and (45)]. On the other hand, the pH of the electrolyte must always be low enough that the inductor is at least 90% protonated, both in solution and as adsorbant. Finally, a buffer must be present so that the protons, necessary for the reaction sequence (42), (43), (45), can be delivered at the electrode. This last condition means that, in case the current density is close to the diffusion-limited value, the molar concentration of the buffer acid must be as high or higher than that of the depolarizer.

All of these conditions were optimized in *Kariv*'s investigation. Strychnine was used as inductor, whose conjugate acid has a pK_a of 7.5, together with an acetate-acetic acid buffer (pH about 4.5) at a concentration of about 0.5 mol/L. *Köster*[57] has shown that the optical yield decreases drastically, on lowering the pH, since the homogeneous-ki-

[*] This experimental finding is also confirmed by calculation of the homogeneous kinetic reaction rate.

[*] With the inductors chosen by *Horner*, which are closely related to ephidrine, the optimal yield is, almost without exception, much lower than with strychnine.

netic protonation, which only yields racemic product, becomes faster with decreasing pH.

It is to be expected that the nature of the cathode material will be decisive for the success of such induced, heterogeneous-kinetic, optically-inductive syntheses. Table 5 gives examples. Whereas mercury and lead cathodes can produce similar, very high, optical yields, the optical yield

Table 5. The dependence of the optical yield (enantiomeric excess e.e.) in the asymmetrically induced synthesis of 1-(2-pyridyl)ethanol with strychnine as inductor on the cathode material. Electrolyte: H_2O/ethanol, 50% vv., 10^{-1}/L HAc + 10^{-1} mol/L NaAc; 10^{-3} mol/L strychnine, 0.5 mol/L 2-acetyl-pyridine, current-density $i = 50$ mA/cm^2.

Electrode material	e.e. [%]	Electrode material	e.e. [%]
Hg	45	Cd	<1
Pb	40	Zn	<1
Bi	10	C	<1
Sb	3		

falls to about 10% at a bismuth cathode, to about 3% at an antimony cathode, and at cadmium, zinc and carbon it is infinitesimally small. It should be mentioned that the optical yield can be correlated with the position of the respective electrosorption equilibria of strychnine. In other respects the order of optical yield corresponds to the order of increasing hydrophobicity from C to Hg presented by *Trasatti*[24, 58–60].

4.2. Anodic Oxidation of Olefins in Non-Aqueous Solutions

4.2.1. The Composition of the Product Mixture on Anodic Oxidation of Styrene in Methanol

Schäfer et al. found that mainly monomers, *i.e.* methyl ethers of 1,2-diols, and dimers, *i.e.* methyl ethers of 1,4-diols, were formed by the anodic oxidation of vinyl compounds in methanol [Eqs. (46) and (47)][61, 62]:

$$C_6H_5CH{=}CH_2 + 2\,HOMe - 2e \rightarrow C_6H_5CH(OMe){-}CH_2OMe + 2H^{\oplus} \quad (46)$$

$$2\,C_6H_5CH{=}CH_2 + 2\,HOMe - 2e \rightarrow (C_6H_5CH(OMe){-}CH_2)_2 + 2H^{\oplus} \quad (47)$$

By investigating the electrode kinetics[*] *Wendt et al.*[27] were able to show that the adsorption of the vinyl compound precedes the charge-transfer step. Thus, an adsorbed radical cation is produced as a reactive intermediate by electron transfer:

$$(C_6H_5CH{=}CH_2)_{solv} \rightleftharpoons (C_6H_5CH{=}CH_2)_{ads} \quad (48a)$$

$$(C_6H_5CH{=}CH_2)_{ads} - e \rightarrow (C_6H_5CH{-}CH_2)^{\oplus\odot}_{ads} \quad (48b)$$

Investigation of the dependence of the product yields on the various parameters showed that solvolysis of the primary radical cation [Eq. (49)] competes with its electrophilic addition to intact olefin [Eq. (50)]; these reactions lead, on the one hand, to the formation of monomeric, methylated 1,2-diol and, on the other, to dimeric, methylated 1,4-diol.

$$(C_6H_5CH{-}CH_2)^{\odot\oplus}_{ads} + (HOMe)_{ads} \xrightarrow[-H^{\oplus}]{k^{het}_{solv}} C_6H_6\overset{\odot}{C}H{-}CH_2OMe \rightarrow \text{monomer} \quad (49)$$

$$(C_6H_5CH{-}CH_2)^{\odot\oplus}_{ads} + (C_6H_5CH{=}CH_2)_{ads} \xrightarrow{k^{het}_{solv}} C_6H_5\overset{\odot}{C}H{-}CH_2{-}CH_2{-}\overset{\oplus}{C}HC_6H_5 \rightarrow \text{dimer} \quad (50)$$

4.2.2. Controlling the Selectivity of the Anodic Oxidation of Styrene

Reactions (49) and (50) occur as surface reactions at the electrode, for vinyl compounds, that are difficult to oxidize (*e.g.* styrene, vinyl ether and butadiene); the rate and selectivity of their reaction depends upon the surface concentration ratios, Γ, of the reactants, under the specific reaction conditions (concentration in the bulk solution, current-density and mass transfer velocity, electrode, electrolyte) [Eqs. (51a)–(51c)]:

$$dN(\text{mono})/dt = k^{het}_{solv}\,\Gamma_{rad\text{-}cat}\Gamma_{HOMe} \quad (51a)$$

$$dN(\text{dim})/dt = k^{het}_{add}\,\Gamma_{rad\text{-}cat}\Gamma_{olef} \quad (51b)$$

$$\eta(\text{dim}) = 1/[1 + k^{het}_{solv}\,\Gamma_{HOMe}/k^{hed}_{add}\Gamma_{olef}] \quad (51c)$$

It is noteworthy that the surface concentration of olefin dissolved in methanol (maximally 1 mol/L) is determined by the adsorption equilibrium constant K^{ads}_{olef}, which depends on the working potential, as well as the concentration of olefin at the electrode surface, which, in turn, depends on the concentration of the olefin in the bulk of the electrolyte, the mass transfer conditions, and the current-density $\Gamma_{olef} = c^{\infty}_{olef}(1 - i/i_d)K_{ads}$.

By taking these factors into account an overall expression can be derived for the yield of dimer[11]. Thus it is possible to predict that the yield of dimer is maximal at negligible current-densities and that it will decrease to zero when the maximum possible, *i.e.* the diffusion-limiting, current is applied[*]. Under diffusion-limited current conditions each olefin molecule reaching the anode by convective diffusion would, of course, be oxidized, so that with diffusion-limited currents there would never be any olefin available at its surface for the coupling reaction [Eq. (50)].

Figure 12 compares the dependence of the dimer yield for anodic oxidation of styrene at a carbon anode on the current-density used—in terms of the diffusion-limited current-density i—with the theoretically deduced value (solid curve). The results in Figure 12 indicate that at sufficiently high styrene concentrations (1 mol/L) and a vanishingly small i/i_d ratio, almost 100% yields of dimer can be obtained[11].

[*] In this case the current-voltage curves do not show "reversible" waves, but are typical for completely irreversible charge-transfer reactions. In such cases the analysis of the current-voltage curves only yields information concerning the kinetics of the charge-transfer and of the reactions which precede the charge-transfer.

[*] This inference is only correct if the dimerization reaction—as alleged—depends on the nucleophilic attack of the radical cation on a, not yet, oxidized olefin molecule. For radical dimerization as competition to solvolysis, on the other hand, the dimer yield would be maximal under diffusion-limited current conditions.

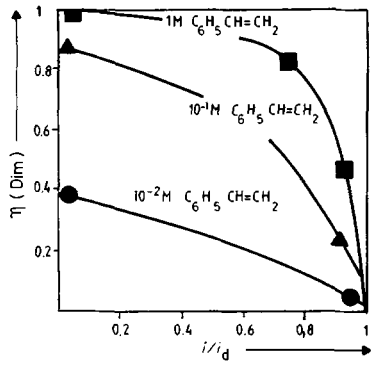

Fig. 12. The dependence of the selectivity (current yield) η for the formation of dimer during the anodic oxidation of styrene at a carbon anode on i/i_d for three styrene concentrations in 0.1 mol/L methanolic $NaClO_4$. The varying yields at negligible current-density ($i/i_d = 0$) correspond to the different surface concentrations Γ of styrene at the C-anode.

In contrast, by using sufficiently low styrene concentrations at current-densities close to the diffusion-limited current-densities, almost 100% selectivity for the monomer is achieved. In principle, it is therefore possible in this case to steer the electrolytic synthesis in either of two directions.

Table 6. The dependence of the relative yield of dimer in the oxidation of styrene on the anode material. Γ_{rel} = relative surface-concentration of styrene. Electrolyte: methanol, 0.1 mol/L $NaClO_4$, 1 mol/L styrene, current-density $i = 50$ mA/cm^2.

Anode material	Rel. yield of dimer	Γ_{rel}
Graphite	1	1
Fe_3O_4	0.2	10^{-2}
PbO_2	0.1	5×10^{-3}
Pt	0.05	2×10^{-3}

Table 6 indicates the strong influence the electrode material has on the olefin electrosorption equilibrium or, to put it another way, the strong relation between the relative rate of the reaction leading to the formation of the dimer, and the anode material. The realizable yields of dimer, under the same electrolytic conditions, are listed in Table 6 for graphite, magnetite, lead dioxide, and platinum anodes, and are compared with the surface concentrations of styrene, calculated from the electrode kinetics[11,21]. This comparison demonstrates that the dimer yield correlates well with the equilibrium constant of the styrene electrosorption.

5. Conclusions and Outlook

The physical chemistry of the electrosynthesis of organic compounds has so far attracted very little interest, for, on the one hand, it has proved difficult to obtain insight into the physicochemical background of such reactions and, on the other, organic chemists are more interested in reactions that "work" than in reactions that do not "work", *i.e.* are not selective enough. However, we are beginning to have a better understanding of the course of such reactions and to recognize what are the most important factors that govern the course and the success of electro-organic syntheses. For all that, the progress made in understanding the individual reactions cannot, as yet, be generalized.

In view of the fact that the industrial electrosynthesis of organic compounds, which had been thought moribund, is finding—albeit modest—application, and further development work in this field is underway, it is to be hoped that the physical chemistry of the reactions involved will, in future, provide the practical chemist with useful ideas, insights and guidelines, and that the synthetic chemist will achieve a better understanding of both his successes and his disappointing results.

I would like to thank those of my co-workers, who are cited in this article, for their work and the results they have made available. Thanks are also due to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the Max Buchner Foundation for supporting most of the investigations forming the basis of this paper which have been carried out at the Technische Hochschule Darmstadt. The enthusiastic help provided by Dr. Köster (Technische Hochschule, Darmstadt) in the final preparation of this article is gratefully acknowledged.

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Hexagonal Ferrites from Melts and Aqueous Solutions, Magnetic Recording Materials

By Hartmut Hibst*

Dedicated to Professor Werner Reif on the occasion of his 60th birthday

Owing to their particular crystallographic properties, ferrimagnetic hexagonal ferrites exhibit a far greater coercive force than the conventional magnetic pigments. They therefore appear to be suitable for use in magnetic information storage procedures, some of which are novel and are at the development stage. Thus, magnetic tapes of high coercive force containing barium ferrite could be used as master tapes for copying magnetic information or for producing forgery-proof magnetic cards, if magnetic heads having high-order write fields were successfully developed. Moreover, platelet-like ferrite pigments in which the preferred direction of magnetic orientation is perpendicular to the plane of the platelet are of great interest for perpendicular magnetic recording.

In this progress report, the crystal structures, magnetic characteristics of hexagonal ferrites, and chemical processes for their production are discussed. In particular, reactions in salt melts or under hydrothermal conditions produce finely divided pigments whose particles have a pronounced hexagonal, plate-like habit, a narrow particle size distribution, and advantageous magnetic properties. The magnetic properties of the pigments crystallized from salt melts may be adjusted by cation exchange.

1. Introduction

"Ferrites" are oxidic solids which have a high proportion of Fe^{III}. The industrially important ferrites are of three different structural types: those having a spinel-type structure, those having a garnet-type structure, and the so-called hexagonal ferrites[1].

Ferrites with a spinel-type structure have the composition MFe_2O_4, where M is, in general, a divalent cation, *e.g.* Mn, Fe, Co, Ni, Cu, Zn, or Cd. In the "normal" spinels, the oxygen ions have a cubic close packed structure; the divalent cations occupy the tetrahedral sites, and the iron(III) ions occupy the octahedral sites. In the "inverse" spinel structure, in contrast, half the iron(III) ions occupy the tetrahedral sites, while the other half occupy the octahedral sites, together with the M^{II} ions. Ferrites which have an inverse spinel structure, or which have structures intermediate between normal and inverse spinel structures, are ferrimagnetic. These solids are used industrially in the form of polycrystalline powders or ceramics, or in the form of monocrystalline epitaxial films or single crystals. The magnetic properties of ferrites are determined to a great extent by their chemical compositions; the presence of even very small amounts of certain impurities or doping substances, which produce substituted ferrites, can cause a pronounced change in the physical properties. Moreover, the magnetic characteristics of the ferrite powders and ceramics are a function of the distribution of the cations in the crystal lattice, of the shape and size of the crystallites and particles, and of their particle size distribution.

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Very finely divided Fe_3O_4 (magnetite) with an inverse spinel structure can be obtained with a mean particle diameter of 50—90 Å by wet-chemical methods, and can thus be processed further to give "magnetic fluids"[2]. By means of "metastable" oxidation, magnetite powders can be converted topochemically, with retention of the crystal habit, into γ-Fe_2O_3, whose spinel type structure has vacancies at tetrahedral and octahedral sites. γ-Fe_2O_3 is currently used on a large scale for the production of magnetic tapes and magnetic disks which are used for the storage of information[3].

Because of their high permeability, and their high electrical resistance in comparison with metallic magnetically soft materials, magnetically soft MnZn ferrites and NiZn ferrites are used for producing magnetic cores. Depending on the composition and the method of production, the magnetic properties of these ferrites may be varied greatly, and thus may be adapted to the particular technical requirements (frequency range, temperature behavior, stability). In general, they are produced by sintering carefully mixed oxides or carbonates. In this process, particularly in the case of Mn-containing ferrites, the splitting off of oxygen on heating and the reoxidation on cooling have to be controlled *via* the partial pressure of the oxygen in the glowing atmosphere. The rate of cooling after sintering may be important, particularly when the distribution of cations in the lattice is very temperature-dependent. Owing to their considerable hardness and their high electrical resistance, these ferrites are also useful materials for magnetic heads used in information storage. By means of vacuum sintering and biaxial or isostatic hot-press techniques, the porosity of the MnZn and NiZn ferrite ceramics can be decreased to less than 0.1% at a particle diameter of *ca.* 10 μm[4]; this makes it possible to produce extremely narrow gaps, and to reduce abrasion of the magnetic head. Monocrystalline MnZn ferrite heads are currently used, in particular, for video recordings. The required MnZn ferrite single crystals are grown by the Bridgman method in platinum crucibles under an atmosphere of oxygen at temperatures above 1600 °C[5].

MnMg ferrites, which are used in toroidal core memories, exhibit a rectangular hysteresis loop at the outset, *i.e.* spontaneously and without orientation of the crystallites, provided they possess the "correct" composition. Because of their high specific electrical resistance, Mg-containing ferrites, in particular, are suitable for microwave applications.

Like the ferrites with a spinel-type structure, those which have a garnet-type structure (composition: $M_3Fe_5O_{12}$, M = Y, Pm, Sm, Eu, Gd, *etc.*) are also of industrial importance. In these structures, which are also cubic, the iron(III) ions occupy tetrahedral and octahedral sites, as in the spinel-type structure; the M^{III} ions are randomly surrounded by eight oxygen ions. Ferrites having a garnet-type structure are employed as magnetic materials for microwave applications. Single crystals, in particular, exhibit advantageous resonance behavior. Ferrimagnetic films which have a garnet-type structure and which have grown epitaxially on nonmagnetic single crystals having a garnet-type or spinel-type structure can form cylindrical, magnetic bubbles when subjected to a magnetic field. This is very important for information storage.

In contrast to the ferrites which have a spinel-type or garnet-type structure, the class of hexagonal ferrites comprises a number of structural types, which are described in more detail in Section 2. The barium and strontium ferrites, which are of very high coercive force and have the magnetoplumbite structure (*M* type, composition: $MFe_{12}O_{19}$, M = Ba, Sr, *etc.*), are now produced industrially in large amounts (world annual production about 70000 tonnes), and are processed further to give permanent magnets[7]. Anisotropic permanent magnetic ceramics which have a higher residual magnetization than isotropic magnets are obtained from "ceramically" produced ferrite powders (cf. Section 4.1) when a magnetic field is applied during shaping to align the magnetic particles of the ferrite powder with their preferred direction of magnetic orientation preferentially in the direction of the field. By far the best degree of orientation is achieved by wet-pressing under the influence of a magnetic field. The pellets are then sintered in air at elevated temperatures (about 1300 °C) to give a magnetic ceramic, and a pronounced anisotropic contraction takes place. Finally, the brittle and very hard crude sintered products are worked with diamond tools, in a cost-intensive process. In contrast, plastoferrite magnets may be produced economically, for example by injection molding, from powders of hexagonal ferrites which are bonded to plastics; although these plastoferrite magnets possess a smaller magnetization than sintered ferrite magnets, they can more readily be processed further by stamping or cutting.

Owing to its high anisotropic field strength, barium ferrite is also a useful material for microwave technology at very high frequencies. The frequency range may be greatly extended by partial substitution of the Fe ions (cf. Section 3.1).

Hexagonal ferrites which have a high proportion of Co, or which are of the *Y* type (see Section 2), possess an almost freely rotatable magnetization vector in the plane of the platelet, perpendicular to the hexagonal *c*-axis, and are accordingly magnetically soft (cf. Section 3.2); they may be used for magnetic cores at very high frequencies.

Furthermore, magnetically hard barium ferrite pigments are important for magnetic recording. The principle of magnetic recording is described in the following[7]: Magnetic tapes and magnetic disks for audio, video and data recording consist of a non-magnetic base and a magnetic storage layer. The magnetic layer contains a magnetic pigment which is uniformly distributed in an organic binder and is in general magnetically orientated. The tape containing the magnetic pigment layer is led past the gap of a horseshoe-shaped iron or ferrite core, the magnetic head of which carries several windings. The information to be stored is converted into an alternating voltage, by means of which, *via* the coil and the core, a magnetic leakage field is produced at the gap, and orientates the magnetic domains of the pigment coating on the tape. The orientation is retained even when the band has left the leakage field.

The strength and permanence of the magnetic recording are determined, in particular, by three parameters: the Curie temperature, the remanent magnetization and the coer-

cive force. The *Curie temperature* is the temperature at which the pigment loses its magnetization as a result of the thermal motion of the spins, and becomes paramagnetic. For practical use, the Curie temperature should be as high as possible. The remanent magnetization and the coercive force are characteristic parameters of the magnetization behavior of a pigment. This behavior is represented as a hysteresis loop. The remanent magnetization M_r is the magnetization remaining when the field has been removed, after magnetic saturation of the pigment by the external magnetic field (M_s = saturation magnetization). The *coercive force* H_c is characteristic of the magnetic field which is required to completely demagnetize the magnetic pigment again, and is a measure of the ability of a pigment to resist demagnetization, *i.e.* to retain the information accepted.

The remanent magnetization and the coercive forces of magnetic pigments are not just material constants of the solids used, but are also greatly influenced by the shape of the pigment particles. The particles of conventional magnetic pigments are acicular, and have a mean particle length of *ca.* 0.5 μm; they consist of ferrimagnetically pure or cobalt-modified γ-Fe_2O_3, or of ferromagnetic CrO_2 or iron[3]. Berthollidic oxides of composition Fe_3O_{4+x} ($x < 0.5$) are also used *inter alia* instead of γ-Fe_2O_3. Whereas magnetic tapes containing pure γ-Fe_2O_3 achieve coercive forces (H_c) of about 30 kA/m, the H_c values of those containing CrO_2 are about 50 kA/m. With cobalt-modified γ-Fe_2O_3 or Fe pigments, H_c values of about 100 kA/m are reached (cf. Fig. 1).

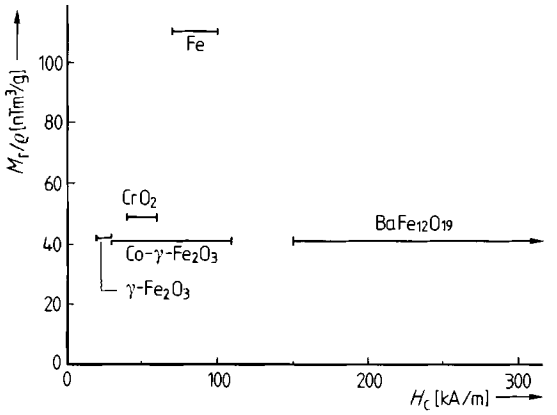

Fig. 1. Coercive force H_c and specific remanent magnetization M_r/ρ of commercially produced magnetic pigments (Fe and CrO_2 non-stabilized; Co-γ-Fe_2O_3 signifies cobalt-substituted γ-Fe_2O_3).

Chromium dioxide is produced hydrothermally by synproportionation of Cr^{III} and Cr^{VI} oxides, and is obtained directly with an acicular particle habit. In contrast, synthesis of acicular, magnetically readily orientatable γ-Fe_2O_3 and Fe pigments with high, defined coercive forces has to be carried out using non-magnetic iron oxide hydroxide (FeOOH) as the starting material; this compound is formed with an acicular habit in the wet-chemical oxidation of iron(II) hydroxide. The resulting FeOOH is dehydrated and reduced with hydrogen at about 350 °C under a defined partial pressure of oxygen to give acicular magnetite (Fe_3O_4), which is converted topochemically into acicular γ-Fe_2O_3 by metastable oxidation. In contrast, the Fe pigment is obtained by reducing FeOOH with pure hydrogen. In the case of γ-Fe_2O_3 and Fe, the art of producing magnetic pigments consists, *inter alia*, in obtaining a magnetic end product with an acicular shape and a particle size which differ very little from those of the non-magnetic FeOOH pigment. High grade magnetic pigments are distinguished by elongated particles of defined size, possess a narrow particle size distribution, are readily dispersible, may readily be oriented in a magnetic field, and have a high chemical stability in the magnetic tape.

Magnetic recordings with carriers containing magnetic pigments of high coercive force should be advantageous in memory technology, particularly at relatively short wavelengths, and this is particularly important for video recording. In addition, an increase in storage density may be expected.

The only pigment of high coercive force ($H_c > 150$ kA/m) which may be used over the whole wavelength without remanent magnetization losses is hexagonal barium ferrite[8] (cf. Fig. 1). In addition, it exhibits desirably low values of the magnetostriction constants[*][9, 10].

Magnetic tapes which have a high coercive force and contain barium ferrite may be used as "master tapes" for copying magnetically stored information[3]. For this purpose, the magnetized master tape is placed in a magnetic field together with unused magnetic tapes of low coercive force, and the information transferred to these tapes.

It is almost impossible to erase magnetically oriented barium ferrite tapes using magnetic fields in the direction of the magnetically hard axis, in contrast to conventional magnetic tapes having the same coercive force[11]. Consequently, it appears that barium ferrite tapes of low coercive force may also be used as master tapes for non-hysteretic contact duplication[12]. In addition, it is thus possible to achieve independent magnetization of each individual layer in dual-layer tapes containing differently oriented barium ferrite layers. Moreover, barium ferrite pigments of high coercive force may be used for producing forgery-proof magnetic cards (credit cards containing strips, identity cards, tickets, *etc.*)[13]. Information carriers of this type are less sensitive to extraneous magnetic fields than the conventional magnetic storage media which have a comparatively low coercive force; in addition, higher packing densities may be employed[14].

However, higher H_c values of the storage layer require magnetic heads with higher gap fields, and the provision of these is difficult due to saturation of the core material. The production of magnetic heads which give sufficiently higher-order write fields remains a thing of the future. Magnetic tapes containing a barium ferrite pigment and having an H_c value of 280 kA/m may still be magnetized if Fe-Co magnetic heads having a high saturation magnetization are used[15]. Suitable alternatives to barium ferrite pigments of high coercive force are $SmCo_5$-metal pigments having an H_c value of 700—900 kA/m. However, even Fe-Co magnetic heads fail to reach such high magnetic fields[16].

Hexagonal barium ferrite is formed as platelets under certain conditions, and the hexagonal *c* axis perpendicular to the plane of the platelet is the easy magnetic direction.

[*] Magnetostriction: Relative elastic change in the length of substance under the influence of a magnetic field (Joule effect).

Thus, barium ferrite would also be suitable as a magnetic pigment for perpendicular recording[*] if it were possible to orient the platelets parallel to the plane of the storage layer. This could be effected either magnetically, as is usual, or mechanically by calendering. Perpendicular recording has advantages over conventional longitudinal recording in processes in which short wavelengths are preferentially stored (video)[8]. In addition it should make very high packing densities possible[17].

As an alternative to particulate barium ferrite layers, non-particulate, magnetically coherent films with vertical anisotropy, for example oxidic barium ferrite or metallic Co-Cr layers applied by a sputtering technique, are suitable for perpendicular recording. It remains to be seen whether it will be possible to produce these films in a sufficiently perfect form, and in the case of the metallic layers, with sufficient resistance to corrosion, or whether particulate barium ferrite layers are more advantageous.

In the following sections the crystal structures and magnetic properties of hexagonal ferrites will be described. Moreover, several chemical methods for the production of finely divided, hexagonal ferrite pigments suitable for the various possible methods of magnetic recording are presented. Salt-melts and hydrothermal syntheses, in particular, give platelet-like pigments having a narrow particle size distribution. By selectively substituting the cations, the magnetic properties of the pigments may be adjusted as desired.

2. Crystal Structures of Hexagonal Ferrites

The crystal structures of the large group of hexagonal ferrites show a number of common features. All structures have a close packed arrangement of oxygen ions, and the barium ions, which are of about the same size, occupy sites analogous to those occupied by oxygen. The substantially smaller M^{II} and Fe^{III} ions occupy the interstitial spaces between the oxygen ions. The magnetoplumbite structure of hexagonal barium ferrite of composition $BaFe_{12}O_{19}$ (M)[18] may be subdivided into so-called M blocks (cf. Fig. 2).

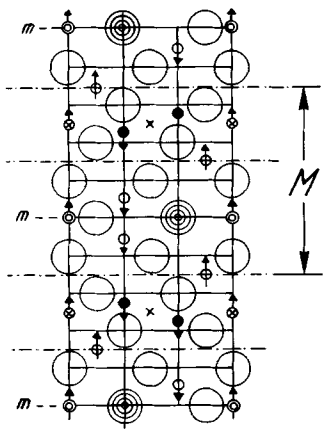

Fig. 2. Cross-section through the magnetoplumbite structure [16] showing an M block and perpendicular c axis. The large blank circles represent oxygen ions and the large filled circles represent barium ions. The small circles associated with arrows represent the distribution of iron(III) ions over the five different sublattice sites, and their spin orientations. Axes of three-fold symmetry are symbolized by lines at right angles, and centers of symmetry by crosses. All layers containing barium ions are located on mirror planes, which have the symbol m.

In these blocks, the Fe^{III} ions occupy five crystallographically different interstitial sites in the oxygen lattice, and some of these sites differ from one another in coordination number. As a result, five magnetic sublattices with different coupling characteristics occur (Table 1)[1].

Table 1. Distribution and spin orientation of the Fe^{III} ions in sublattice sites of $BaFe_{12}O_{19}$ [1].

Sublattice	12k	$4f_1$	$4f_2$	2a	2b
Site	Octahedral	Tetrahedral	Octahedral	Octahedral	Trigonal bipyramidal
Coordination	6	4	6	6	5
Number of Fe^{III}-ions per M Block	6	2	2	1	1
Spin	↑	↓	↓	↑	↑

Another hexagonal ferrite, $Ba_2M_2Fe_{12}O_{22}$(Y), is composed of Y blocks[19,20]. In the blocks, only tetrahedral and octahedral sites are occupied by cations.

The large number of other hexagonal ferrites may be subdivided into two structural families[21]. One relatively large family comprises stacking variations M_pY_n in which the structural building blocks M and Y are stacked along the hexagonal c axis in different, but generally regular, sequences (Table 2).

Table 2. Hexagonal ferrites with M_pY_n stacks [a].

$M:Y$	Stacking sequence	Ideal composition	Symbol
2 : 1	M_2Y	$Ba_4M_2Fe_{36}O_{60}$	U [22]
2 : 2	$MYMY$	$Ba_6M_4Fe_{48}O_{82}$	Z [19]
2 : 3	$MYMY_2$	$Ba_8M_6Fe_{60}O_{104}$	
2 : 4	$MYMY_3$	$Ba_{10}M_8Fe_{72}O_{126}$	
2 : 4	MY_2MY_2		
4 : 3	$MMYMYMY$	$Ba_{10}M_6Fe_{84}O_{142}$	
4 : 5	$MYMYMYMY_2$	$Ba_{14}M_{10}Fe_{108}O_{186}$	
4 : 8	$MYMYMY_3MY_3$	$Ba_{20}M_{16}Fe_{144}O_{252}$	
4 : 8	$MYMYMY_2MY_4$		
4 : 8	$MYMY_2MY_2MY_3$		
4 : 33	$MY_6MY_{10}MY_7MY_{10}$	$Ba_{70}M_{66}Fe_{441}O_{802}$	
6 : 13	$MYMYMYMY_2MY_3MY_5$	$Ba_{32}M_{26}Fe_{228}O_{400}$	
6 : 14	$MYMYMY_2MY_3MY_2MY_5$	$Ba_{34}M_{28}Fe_{240}O_{422}$	
8 : 27	$M_3Y_4MY_7MYMYMY_6MY_8$	$Ba_{62}M_{54}Fe_{420}O_{746}$	

[a] In addition to the structures listed above, 35 other M_2Y_n structures and 6 M_4Y_n structures are known.

The unit cell of M_4Y_{33}, which contains 4100 atoms and has a volume of 47000 Å^3 (c = 1577 Å), is one of the largest cells of all known inorganic compounds[21].

The second, smaller structural family M_nS is obtained by stacking M layers with structural elements (S) from the cubic spinel-type structure MFe_2O_4 (Table 3).

Whereas it has been possible to determine the structures of the majority of the stacking variations by single crystal X-ray methods[25-28], electron-optical methods of investiga-

[*] Perpendicular recording: In conventional longitudinal recording, the direction of easy magnetization lies in the plane of the magnetic tape, in its direction of travel. In contrast, perpendicular recording is possible only with a medium with magnetic anisotropy perpendicular to the plane of the medium.

Table 3. Hexagonal ferrites with M_nS stacks.

M : S	Stacking sequence	Ideal composition	Symbol
1 : 1	MS	$BaM_2Fe_{16}O_{27}$	W [19, 23, 24]
2 : 1	M_2S	$Ba_2M_2Fe_{28}O_{46}$	X [19]
4 : 1	M_4S	$Ba_4M_2Fe_{52}O_{84}$	
6 : 1	M_6S	$Ba_6M_2Fe_{76}O_{122}$	

tion were employed in addition, particularly for the very complicated structures[21,29]. Moreover, it has recently been possible to determine the structures of other exotic "intergrowth phases" M_pY_n by direct, lattice-imaging and high resolution transmission electron microscopy[30,31-33].

Of the large number of known structures, only the basic compounds M ($BaFe_{12}O_{19}$) and Y ($Ba_2M_2Fe_{12}O_{22}$), and the stacking variations having comparatively simple structural patterns (U, Z, W and X) are obtainable as powders in relatively large amounts and can thus be identified on the basis of their X-ray powder diagrams[34]. The relatively simple basic structures M and Y are formed at 800 and 950 °C, respectively, and the stacking variations only at 1150—1300 °C[35].

The other compounds listed above, which have more complicated structures, were isolated only as small single crystals from multi-phase ferrite preparations, powders being obtained from various melts by crystallization[36,37]. It has hitherto been impossible to find a relationship between the conditions of synthesis and the intergrowth phases obtained.

In an analogous system containing strontium instead of barium, only the M, W[38,39], and X phases[40] have been found to date.

3. Magnetic Properties

3.1. Magnetic Properties of $BaFe_{12}O_{19}$

$BaFe_{12}O_{19}$ has a highly anisotropic, hexagonal crystal structure and an anisotropy constant K_1 of 330 kJ/m³[1], and therefore exhibits high magnetocrystalline anisotropy[*], the hexagonal axis being a very strongly preferred direction for the magnetic moment. In platelet-like barium ferrite crystals, the direction of easy magnetization and the hexagonal c axis are perpendicular to the plane of the platelet.

The anisotropic field strength H_A, which specifies the magnetic field theoretically required to simultaneously reverse all spins in a saturated, monocrystalline material, is a measure of the material-specific magnetic rigidity. For $BaFe_{12}O_{19}$, an anisotropic field strength of $H_A = 2K_1/M_s = 1330$ kA/m is obtained. Accordingly, the maximum obtainable coercive force of an isotropic, magnetically non-orientated barium ferrite powder containing magnetic single-domain particles is $H_c = 0.48 \cdot H_A$[41] = 640 kA/m. This value is further decreased by a maximum of 30% by the contribution from anisotropy of shape of the platelet, which has not been taken into account[42]. This contribution depends on the diameter/thickness ratio of the platelet. In addition, the dependence of the coercive force on the density of packing of the pigment must be taken into account[43-45]. Since both the anisotropy constant K_1 and the saturation magnetization M_s decrease uniformly with increasing temperature, H_A, and therefore also the coercive force H_c, are almost temperature-independent up to about 250 °C[1]. The extremely low h_{25} value of only 0.13 is calculated as the switching field distribution[*] for an isotropic distribution of the particle directions[46].

The saturation magnetization M_s is of the same order of magnitude as in other ferrimagnetic iron oxides, and is 478 mT at room temperature.

3.1.1 Decreasing the Coercive Force H_c by Milling Processes

The coercive force actually attained is always smaller than the calculated maximum value. Particularly when barium ferrite powders are milled, the H_c values are greatly reduced (to about 130 kA/m). This is essentially caused by the fact that lattice defects occur in pigment particles when a material is intensively milled[47-50]; however, a small proportion of the decrease in H_c on milling must be attributed to the presence of very fine superparamagnetic constituents[51,52] and to the considerably disturbed surface of the powder particles[50]. The coercive force increases to a maximum of about 350 kA/m on subsequent tempering, and this increase may be explained by the elimination of the lattice defects[47,48] and the combination, by sintering, of the very fine superparamagnetic particles to give larger magnetic single-domain particles[51].

3.1.2. Adjustment of the Magnetic Properties by Substitution

Milling and tempering processes are not the only means of adjusting the coercive force of a barium ferrite powder; it is also possible to change the value of the anisotropy constant K_1 by substitution. The resulting magnetocrystalline anisotropic field strength H_A and the maximum coercive force H_c achievable therewith are, in general, proportional to K_1/M_s. Substitutions have been carried out, *e.g.* on hexagonal ferrites, to adjust the resonance frequency, *via* H_A, to a particular value for high frequency applications[53,54].

Thus, the barium ions in $BaFe_{12}O_{19}$ may be completely replaced by strontium ions[38,55-58] or by lead ions[38,55], or partially replaced by calcium ions[38,55,59-64]. $SrFe_{12}O_{19}$ has an anisotropy constant ($K_1 = 357$ kJ/m³[57]) which is 10% higher than that of barium ferrite, and is therefore particularly suitable for applications requiring high coercive forces. The alkaline earth ions may also be substituted by cation pairs M^I-M^{III} (M^I = Na, K, Rb, Ag, Tl; M^{III} = La, Pr, Nd, Sm, Gd)[65,66].

[*] Magnetocrystalline anisotropy: Crystal anisotropy is associated with crystal energy. This is the energy required to rotate the magnetization vectors from the preferred direction of easy magnetization to the direction of difficult magnetization.

[*] Switching field distribution (h_{25}): Each particle of a magnetic pigment has its direction of magnetization reversed in a magnetic counter-field at a slightly different field strength, which is dependent, for example, on the particle shape and size and the defect concentration. A magnetic pigment containing very similar particles, *i.e.* having a very narrow distribution of particle size, has in consequence a narrow switching field distribution with a small h_{25} value and a comparatively steep ascent of the hysteresis curve. For an exact definition see [152, 153].

The Fe^{III} ions may be replaced by Al^{III} [56, 59, 67–78], Ga^{III} [59, 70, 72, 73, 76–80], Cr^{III} [59, 70, 72, 73, 76, 81–83], In^{III} [76, 77, 84–86], Sc^{III} [77, 85, 87], or Ru^{III} ions[88]. In all cases, the Curie temperature, the saturation magnetization, and the residual magnetization decrease with increasing degree of substitution. The pronounced increase in the coercive force observed on substitution by Cr^{III} and Ga^{III} may be attributed to an increase in the critical single-domain size[76, 83]. Substitution by aluminum additionally gives rise to an increase in the coercive force, owing to an increase in the anisotropic field strength. Indium and scandium ions preferentially occupy sites having trigonal bipyramidal coordination spheres in the crystallographic sublattice 2b, resulting in a pronounced decrease in the anisotropy constants; this gives rise to special magnetic block structures or helical structures[77].

Hexagonal *M* ferrites are also known in which the Fe^{III} ions are partially replaced by a combination of ions of different valencies, giving rise to solids of compositions $BaM^{II}_xM^{IV}_xFe_{12-2x}O_{19}$ and $BaM^{II}_{2x}M^{V}_xFe_{12-3x}O_{19}$. The following cation pairs have been used to date: Zn^{II}-Ti^{IV}[1, 89–93], Ni^{II}-Ti^{IV}[1, 93], Co^{II}-Ti^{IV}[1, 74, 93–100], Cu^{II}-M^{IV}[101], Fe^{II}-Ti^{IV}[102], M^{II}-Zr^{IV}[66], Zn^{II}-Ir^{IV}[103], Zn^{II}-Ge^{IV}[76, 81], M^{II}-Sn^{IV}[66], Zn^{II}-V^{V}, Zn^{II}-Nb^{V}, Zn^{II}-Ta^{V}[76, 81], Cu^{II}-M^{V}[101] and Fe^{II}-Sb^{V}[102]. In all cases, the anisotropy constant, the anisotropic field strength and the coercive force decrease with increasing substitution, the greatest effect being obtained for Co^{II}-Ti^{IV} and Zn^{II}-Ir^{IV}. Thus, the uniaxial anisotropy in the direction of the hexagonal *c* axis vanishes on substitution by Co^{II}-Ti^{IV} for $x > 1.2$[1], and on substitution by Zn^{II}-Ir^{IV} for $x > 0.3$[103], the easy direction of magnetization being tilted in the plane of the crystal platelet perpendicular to the crystallographic *c* axis. In virtually all systems, the Curie temperature and the saturation magnetization decrease with increasing x. A deviation from this behavior was found with Co^{II}-Ti^{IV} substitution, where the saturation magnetization was found to decrease only slightly[1, 74, 95], or even to remain constant[99, 100], in the area of uniaxial anisotropy. For a low degree of substitution by Zn^{II}-Nb^{V}, the magnetization even increases[81]. In the system $BaM_xTi_xFe_{12-2x}O_{19}$, a pronounced temperature dependence of the anisotropic field strength is obtained when M is Co, in contrast to the case where M is Zn or Ni; with Cu, it is possible to achieve a remanent magnetization which is less temperature dependent[101].

Furthermore, it is possible to simultaneously replace Ba^{II} by M^{III} (Y[104], La[102, 104–108], Pr[105, 106], Nd[105], Sm[104, 105], or Eu[105]) *and* Fe^{III} by M^{II} (Co, Ni[106] or Fe). In the system $Ca^{II}_{1-x}La^{III}_xFe^{III}_{12-x}Fe^{II}_xO_{19}$, it is possible to produce magnetically hard ceramics possessing magnetic properties similar to those of barium ferrite[109, 110]. Finally, mixed crystals of composition $BaCo^{II}_xFe^{III}_{12-x}O_{19-x}F_x$ have also been described[111].

3.2. Magnetic Properties of Other Hexagonal Ferrites

In *Y* ferrites of composition $Ba_2M^{II}_2Fe^{III}_{12}O_{22}$ (M^{II} = Mn, Fe, Co, Ni, Zn or Mg), the direction of spontaneous magnetization lies in the platelet plane perpendicular to the hexagonal *c* axis, and is virtually freely rotatable in this preferred plane[112]. These ferrites are therefore magnetically soft and are unsuitable as materials for permanent magnets or magnetic pigments. However, *Y* ferrite is of interest for high-frequency applications[113]. In *Y* ferrites when M is Co the preferred directions of magnetization form a cone with the *c* axis as cone axis at low temperatures[17]. When M is Cu, the *Y* ferrite is magnetically uniaxial at room temperature[114].

The remaining hexagonal ferrite phases *U*, *Z*, *W* and *X*, which may be regarded as stacking variations of the basic structures *M* and *Y*, or *M* and *S* (cf. Section 2) are, like the *M* phase, magnetically uniaxial when M^{II} is Mn, Fe, Ni, Zn, Mg, Cu, or $(Li^{I}+Fe^{III})/2$. The anisotropy constant and the saturation magnetization are dependent on the particular structure and on the M cations, but are in general lower than those of the *M* ferrite[1, 115, 116]. Only the *W* structure with M = Zn has a higher saturation magnetization than the *M* phase[116]. The anisotropic field strength is decreased in all cases by increasing substitution of the M cations by Co, until the uniaxial anisotropy finally becomes planar anisotropy[1, 98, 117, 118]. In the structure Co_2Z ($Ba_3Co_2Fe_{24}O_{41}$) at low temperatures, the preferred directions of the magnetization vector form a cone. In addition, the magnetic properties of the particular ferrite phases may be varied by other substitutions, for example by substituting Fe^{III} ions by Al, Ga, In, or Sc[69, 119], as already investigated in detail for $BaFe_{12}O_{19}$ (*M*).

In order to determine which of the crystallographic sites are occupied in the ferrites obtained by substitution of cations, and to explain the altered magnetic properties, Mössbauer spectroscopy has been used in many cases[75, 79–82, 85, 91, 92, 107, 108, 120, 121].

4. Process for the Production of Powders of Hexagonal Ferrites

4.1. "Ceramic Process"

M-barium ferrite powder, which is processed further, for example, to give plastoferrites, is conventionally produced by the ceramic process. In this process, a mixture of $BaCO_3$ and synthetic or mineral iron(III) oxide in the form of granules is calcined at high temperature (1200–1350 °C) in a rotary tubular kiln. The resulting sintered crystalline agglomerates of $BaFe_{12}O_{19}$ are broken down by a milling process into individual magnetic single-domain particles having a diameter of about 1 μm. The intensive milling required gives rise to crystal structure defects resulting in a comparatively low coercive force. The defects are eliminated in part by tempering, as a result of which the H_c values may increase to a maximum of 350 kA/m (cf. Section 3.1.1). The relatively low coercive forces result from hysteresis characteristics which are determined predominantly by nucleation[122].

The production of the other hexagonal ferrite ceramics is carried out using a similar process, the additionally required M^{II} cations being provided, in general, by using the appropriate oxides or carbonates in the starting mixture.

Ceramic ferrite powders do not appear to be very suitable for use in recording media. Particularly disadvantageous are the particle coarseness, the broad particle size

distribution (cf. Fig. 3) caused by the milling process, and the poor switching field distribution of the powder.

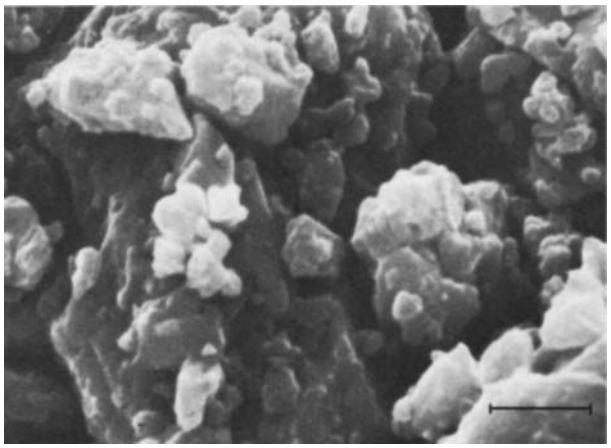

Fig. 3. Ceramically produced and milled barium ferrite (*M*) (the distance indicated corresponds to 1 μm).

4.2. Coprecipitation and Tempering

In contrast to production of ceramics, the coprecipitation process produces finely divided barium ferrite preparations[42, 123–125]. In this process, an aqueous solution of barium chloride and iron(III) chloride is stirred into an excess of an aqueous solution of sodium hydroxide or sodium carbonate. The product of coprecipitation is filtered off, washed thoroughly and dried. Barium ferrite of very high coercive force, with an H_c value of about 450 kA/m, is obtained on tempering, even at 925 °C. The average particle diameter is *ca.* 0.1—0.2 μm (cf. Fig. 4), and the particle size distribution is comparatively narrow. In addition, the coercive force of the ferrites is less temperature-dependent than that of the ceramically produced and milled powders. Microwave absorption spectra have shown that the hysteresis process in the materials obtained by coprecipitation and tempering is determined predominantly by coherent rotation, whereas the reversal of magnetization by nucleation only plays a minor role[126].

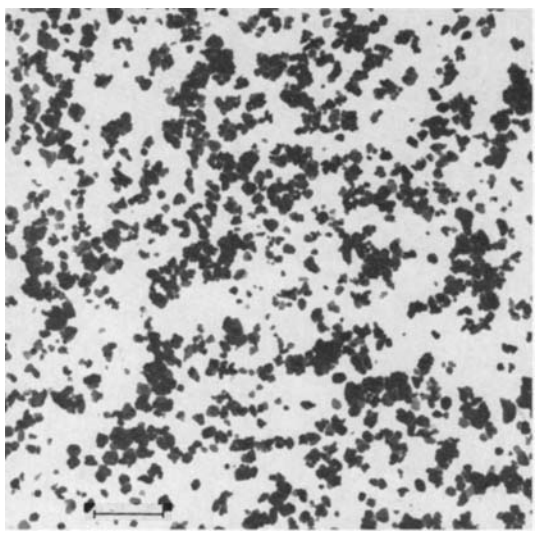

Fig. 4. Finely divided barium ferrite prepared by coprecipitation and tempering (1 h, 925 °C) (the distance indicated corresponds to 1 μm).

In spite of the low reaction temperature in our experiments, the ferrite material is highly agglomerated or even partially sintered. As with the products of the ceramic process, this material requires milling to make it suitable for use as a magnetic pigment. Such a process must be regarded as critical, even when less intensive milling is sufficient. Thus, by means of microwave resonance it could be established that even when the barium ferrite material obtained after tempering is ground gently in a mortar, the number of crystal defects increases, favoring, in turn, noncoherent hysteresis processes[127].

4.3. Synthesis from Melts

4.3.1. Oxidic Fluxes

The growth of $BaFe_{12}O_{19}$ single crystals from BaO-Fe_2O_3 melts (molar ratio 1 : 6) presents problems at atmospheric pressure, owing to the high melting point and elimination of oxygen[23]. The evolution of O_2 begins above 1450 °C, the *M* ferrite decomposing peritectically to form the iron(II)-containing *X* phase. Barium ferrite without an iron(II)-constituent can be crystallised out congruently from a melt at 1540 °C only at a pressure of oxygen of 40 bar or more[128].

The melting point may be lowered by increasing the proportion of Ba or by addition of other oxides, so that Fe^{II} free ferrites may also be obtained at atmospheric pressure. Thus, *Stuijts* has grown large platelet-like single crystals of $BaFe_{12}O_{19}$ by slowly cooling a virtually eutectic BaO-Fe_2O_3 melt[129].

Relatively large $BaFe_{12}O_{19}$ single crystals can be obtained from BaO-Na_2O-Fe_2O_3 melts, even at temperatures below 1250 °C[130]. By adding other oxide components, substituted barium ferrites[65, 70] and other hexagonal ferrite single crystals have also been obtained[36, 37, 131].

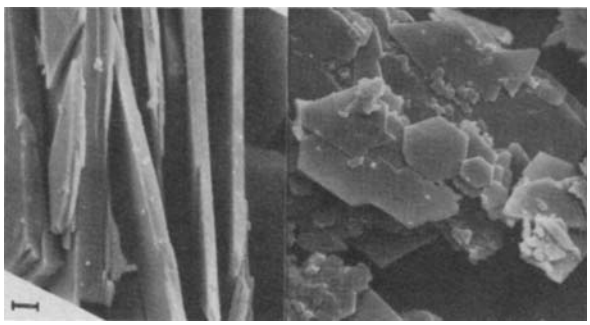

Fig. 5. Magnetically oriented, hexagonal ferrite powder obtained from boric acid melts (the distance indicated corresponds to 2 μm). The magnetic field runs horizontally from left to right in both cases. Left: $BaFe_{12}O_{19}$ (*M*); the preferred direction of magnetization is perpendicular to the plane of the platelet. Right: $Ba_2Zn_2Fe_{12}O_{22}$ (*Y*); the preferred direction of magnetization is in the plane of the platelet.

In addition, the crystals' qualities may be improved by using melts of the system BaO-B_2O_3-Fe_2O_3 (cf. Fig. 5). These melts are advantageous since they possess low volatility, low viscosities, low melting points, and have a negligible corrosive effect on Pt crucibles. Better crystallized

monocrystalline hexagonal ferrites which have only a small number of flux occlusions are obtained[37, 132–135].

Relatively large barium ferrite crystals may be grown by adding PbO and PbF_2 to the BaO-B_2O_3-Fe_2O_3 system, but this flux presents considerable problems due to its high volatility, density, rate of corrosion of Pt, and toxicity[136, 137]. Furthermore, substituted barium ferrites have been crystallized from melts having a high proportion of bismuth oxide[103].

Single crystals of hexagonal ferrites, of considerable size in some cases, have been crystallized from the above melts either by "top seeding" methods of crystal growth or by spontaneous nucleation by very slow cooling. Moreover, ferrimagnetic hexagonal ferrite layers can be grown epitaxially on non-magnetic monocrystalline substrates, particularly from melts containing boric acid, lead oxide, or lead fluoride. The resulting solids are of interest for microwave applications and for use in memories[138, 139].

Inorganic pigments may also be obtained from fluxes[140], the melts being quenched to give amorphous products. When the resulting glass is tempered, the pigment particles crystallize out spontaneously and homogeneously, the particle size in general increasing with temperature. The pigments are subsequently isolated by dissolving the matrix.

Using this process, barium ferrite pigments of high coercive force and narrow particle size distribution may be produced from BaO-B_2O_3-Fe_2O_3 melts[141–143]. A special technique which has been developed for the production of amorphous metals[144] and makes a maximum quenching rate of 10^6 K per second possible is required in this case to quench the above melts to produce amorphous products. This is achieved by pouring the boric acid melt between two metal rollers which are pressed together and rotate very rapidly in opposite directions; the melt is quenched by these rollers to give a glass band about 0.1 mm thick. After the amorphous bands have been tempered at about 850 °C and undergone aftertreatment with acetic acid, a barium ferrite pigment of very high coercive field ($H_c = 425$ kA/m), narrow particle size distribution, and platelet diameter of the order of 0.5 μm is obtained in virtually theoretical yield, based on Fe^{III}. Since the pigment particles crystallize out without being in contact with one another, slightly agglomerated, non-sintered powders are obtained, making it possible to dispense with subsequent milling which causes damage. By introducing other oxides into the boric acid melt, pigments of substituted barium ferrite suitable for magnetic recording are obtained after quenching, tempering, and washing out[145]. A similar method was also subsequently described for the BaO-Na_2O-Fe_2O_3 system[146].

4.3.2. Salt Melts

Alkali metal- and alkaline earth metal-chlorides in the molten state possess a high dissolving power for iron(III) oxide and other oxides[147], and this solubility may be used for growing relatively large single crystals or finely divided pigments. Thus, single crystal platelets of barium ferrite of about 1 mm size are obtained by introducing iron(III) oxide into molten barium chloride or barium fluoride at 1200–1300 °C in the presence of moist oxygen[148, 149]. It is also possible to convert mixtures of $BaCO_3$ and iron oxide hydroxide (FeOOH) in alkali metal salt melts at 1000 °C into barium ferrite powders. By dissolving the alkali metal chloride matrix, barium ferrite platelets of about 1.5 μm diameter with a maximum coercive force of 280 kA/m are obtained[150]. An improved process employs a dispersion of iron oxide hydroxide in aqueous NaCl-KCl, the dispersion being produced by precipitation from an iron(III) chloride solution using solutions of sodium hydroxide and potassium hydroxide, and subsequent heating. Thereafter, solid $BaCO_3$ is added, and a mixture of $BaCO_3$, FeOOH, NaCl, KCl is obtained after spray-drying. Relatively coarse-grained pigments (platelet diameter about 1.0–1.5 μm) are again formed at the temperatures (1000–1050 °C) required for quantitative formation of the ferrite, but these pigments exhibit better H_c values (425 kA/m)[151].

Finely divided products of very high coercive force are obtainable by a novel method which combines the advantages of the coprecipitation process (see Section 4.2) and the salt flux process, and at the same time avoids their disadvantages[152, 153]. Thus, when spray-dried NaCl-containing coprecipitates are heated, single-phase barium ferrite preparations with high H_c values (about 450 kA/m) and small platelet diameters (0.1–0.2 μm) are obtained at remarkably low temperatures (≥730 °C). The pigment particles crystallize from the NaCl matrix as a monodispersion with a pronounced hexagonal platelet habit and narrow particle size distribution, each platelet being separated from its neighbors by a salt layer. After the NaCl has been dissolved in water, a very finely divided, readily dispersible, non-sintered, loose powder is obtained, thereby obviating disadvantageous milling processes to produce more finely divided particles (cf. Fig. 6).

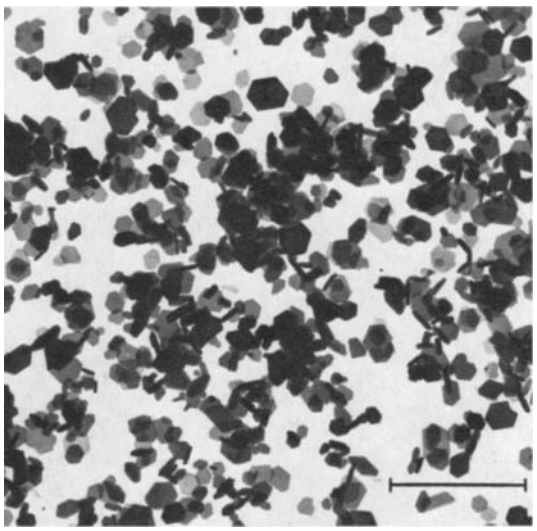

Fig. 6. Finely divided barium ferrite pigment of high coercive force, obtained from an NaCl flux ($H_c = 450$ kA/m; the distance indicated corresponds to 1 μm).

The switching field distribution ($h_{25} = 0.15$) is favorably low and almost reaches the theoretical value of 0.13, indicating a still lower contribution compared to the products obtained by coprecipitation and tempering from undesira-

ble processes involving noncoherent reversal of magnetization. By changing the composition of the coprecipitate, substituted ferrites of type *M* can also be obtained. Thus, magnetic pigments having good properties have been obtained in the $BaM_xTi_xFe_{12-2x}O_{19}$ (M = Zn, Ni, or Co) system, a low defined coercive force being established by altering the degree of substitution (cf. Fig. 7). In addition, magnetically soft *Y* ferrites, crystallizing in pronounced platelet form, are obtainable as powders even at 900 °C[154]. It is remarkable that all other hexagonal ferrite phases are obtained only at higher temperatures, even by this reaction-promoting process[35].

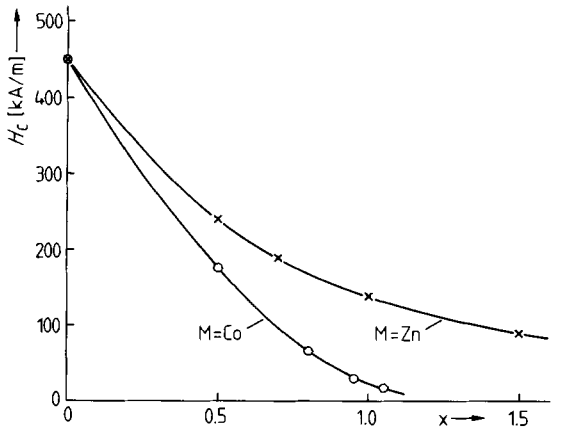

Fig. 7. Variation of the coercive force H_c with the degree of substitution x for $BaM_xTi_xFe_{12-2x}O_{19}$ pigments, where M = Co or Zn.

Platelets of hexagonal ferrites of the *M* and *Y* type may also be produced in a simple manner by directly tempering salt mixtures comprising $BaCO_3$, MCO_3 (*e.g.* "Zn hydroxide carbonate"), $FeCl_3$, Na_2CO_3, and K_2CO_3[155, 156]. In this reaction, finely divided, reactive iron(III) oxide is formed as an intermediate and is continuously dissolved in the eutectic NaCl-KCl melt which forms simultaneously, thus supplying further reaction components. Substituted ferrites are also accessible, and Figure 8 shows a platelet-like *Y* ferrite ($Ba_2Zn_2Fe_{12}O_{22}$).

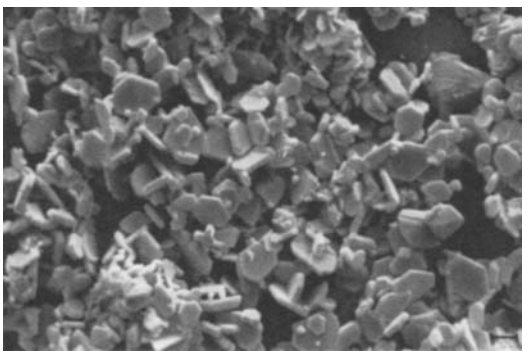

Fig. 8. $Ba_2Zn_2Fe_{12}O_{22}$ (*Y*) obtained by direct tempering of intimate [$BaCO_3$-("Zn-hydroxide carbonate")-$FeCl_3$-Na_2CO_3-K_2CO_3] salt mixtures (the distance indicated corresponds to 2 μm).

In the case of other educts, the two last-mentioned flux processes permit production of ferrite powders with spinel-type structures[157, 158]. Recently other nonmagnetic inorganic solids, *e.g.* lithium aluminate, barium titanate, and alkali metal niobates, have been obtained from alkali metal chloride melts. Ferroelectric lead niobate ceramics containing oriented crystals may be obtained by preparing $PbNb_2O_6$ needles from a eutectic NaCl-KCl melt, followed by doctor blade casting and tempering[159].

In addition to the halides, alkali metal sulfates are also important reaction-promoters for the synthesis of barium ferrite. Thus, $BaCO_3$-Fe_2O_3 mixtures may be converted quantitatively in the presence of a eutectic Na_2SO_4-K_2SO_4 melt at 950 °C into $BaFe_{12}O_{19}$[160]. The disadvantage of this procedure, however, as our own experiments have shown, is that the required excess of barium always forms poorly soluble $BaSO_4$[152].

4.4. Hydrothermal Synthesis of Barium Ferrite Powders

In the hydrothermal preparation of barium ferrite of composition $BaFe_{12}O_{19}$, a dispersion of iron(III) oxide, iron(III) hydroxide, or iron(III) oxide hydroxide is heated for a few hours in an aqueous solution of barium hydroxide to temperatures above the boiling point and below the critical point of water (374 °C). Whereas Fe_2O_3 was initially used as the educt[161], it was possible soon thereafter to obtain improved ferrite preparations by using α-FeOOH (goethite)[162–166]. By this means it is possible to produce barium ferrites having a pronounced platelet habit and mean crystal diameters of about 0.5–2 μm, temperatures above 200 °C being required. The platelet size is dependent on the fineness of the α-FeOOH particles used, and increases with increasing reaction temperature; the crystal diameter may be reduced by using a large excess of barium[166]. According to our own experiments, the products have an extremely broad particle size distribution (see Fig. 9), resulting in a poor switching field distribution.

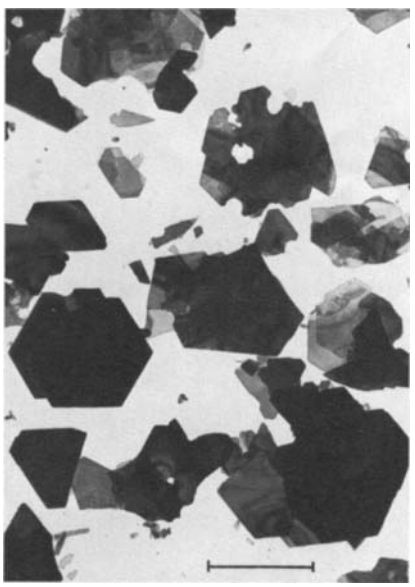

Fig. 9. Hydrothermally produced (300 °C, 8 h, Fe/Ba = 7.9) barium ferrite $BaFe_{12}O_{19}$ obtained from α-FeOOH and $Ba(OH)_2$; specific BET surface area (A_{N_2}) = 3.2 m^2/g (the distance indicated corresponds to 1 μm).

A more recent hydrothermal process starts from $Ba(NO_3)_2$-$Fe(NO_3)_3$-NaOH and involves coprecipitation with excess sodium hydroxide solution[165–167]. Single-

phase, α-Fe_2O_3-free barium ferrite preparations are obtained only in the presence of a small excess of Ba. The required reaction temperature is 150—180 °C, and decreases with increasing alkali concentration. It is remarkable that the particle size may be controlled not only by means of the temperature and the duration of the reaction, but also *via* the barium and NaOH concentrations. Both a high excess of barium and a high excess of NaOH produce, at 160—280 °C, a drastic decrease in the platelet diameter owing to an increased rate of nucleation, and the preparations are obtained with the desired high specific surface areas (cf. Fig. 10)[168]. Unfortunately, the decrease in particle size entails lower coercive forces and specific remanent magnetization and saturation magnetization (cf. Fig. 11). As a result, the material has to be tempered at 500—800 °C to improve the magnetic properties; however, an increase in particle size must be accepted. At 850—1050 °C, maximum H_c values of about 380 kA/m and theoretical values for the magnetizations are attained.

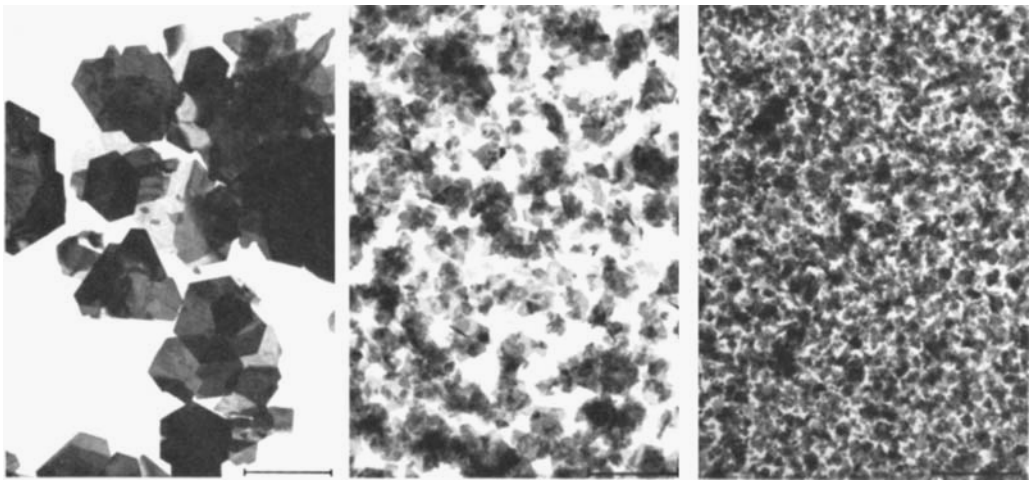

Fig. 10. Hydrothermally produced barium ferrite $BaFe_{12}O_{19}$ obtained from $Ba(NO_3)_2$-$Fe(NO_3)_3$-NaOH coprecipitates (200 °C, 5 h). Left: Fe/Ba = 8.0; NaOH excess = 80 g/L (A_{N_2} = 9 m^2/g). Middle: Fe/Ba = 8.0; NaOH excess = 330 g/L (A_{N_2} = 54 m^2/g). Right: Fe/Ba = 2.9; NaOH excess = 80 g/L (A_{N_2} = 70 m^2/g) (the distance indicated corresponds to 1 μm).

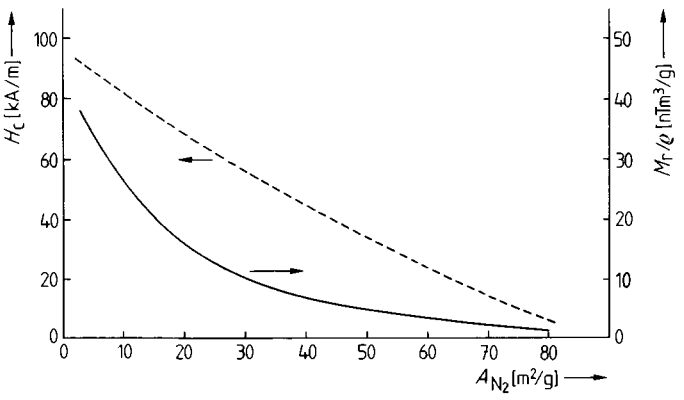

Fig. 11. Decrease in the coercive force H_c (---) and the specific residual magnetization M_r/ρ (—) in hydrothermally produced barium ferrite pigments as a function of the surface area A_{N_2}.

At higher temperatures (300—350 °C), low as well as high concentrations of NaOH give coarse-grained pigments in the hydrothermal process. However, it is remarkable that preparations produced in the presence of high NaOH concentrations are of comparatively high coercive force (almost 300 kA/m) after tempering at 1100 °C, while the powders obtained at low NaOH concentrations give H_c values of only 150 kA/m[168]. The differences in the coercive force may be explained by the narrower particle size distribution of the preparations obtained in the presence of high NaOH concentrations. The hydrothermal production of a substituted *M* ferrite, or of other hexagonal ferrites, has not been described to date.

The hydrothermal synthesis of single-phase $BaFe_{12}O_{19}$ may be complicated by the occurrence of other phases; for example, very finely divided, non-ferrimagnetic particles of composition $BaO \cdot 4.5\,Fe_2O_3$ are formed in the lower temperature range (< 180 °C)[165, 166, 169]. In the preparation of the ferrite from γ-FeOOH and $Ba(OH)_2$, this compound ($BaO \cdot 4.5\,Fe_2O_3$) is formed at the temperature at which γ-FeOOH is usually converted to the α-modification. $BaO \cdot 4.5\,Fe_2O_3$ is also obtained in a well crystallized form by passing air into a strongly alkaline $BaCl_2$-$FeCl_2$-NaOH coprecipitate at atmospheric pressure[170]. Antiferromagnetic hexagonal $BaFe_4O_7$ can be synthesized hydrothermally at 250—300 °C, under a high partial pressure of oxygen[165, 171–174]. Using high concentrations of barium and NaOH, it has recently been possible to isolate a novel metastable compound of composition $BaFe_6O_{10}$ in the form of fine hexagonal platelets[175] (see Fig. 12). The pigment is nonmagnetic and appears to be of interest for producing transparent reddish-orange hues.

Hydrogen may be formed by corrosion when the hydrothermal synthesis is carried out in a steel autoclave, particularly at temperatures in the upper part of the range, and when relatively long reaction times are used. Under the resulting reducing conditions, Fe^{II}-containing ferrites, such as antiferromagnetic $[Ba_8Fe^{II}(OH)_6][Fe^{III}_{12}O_{24}]$[176] and ferrimagnetic $Ba_4[Fe^{III}(OH)_6][Fe^{II}Fe^{III}_7O_{14}]$[177], are formed.

The crystal structure of $[Ba_8Fe^{II}(OH)_6][Fe^{III}_{12}O_{24}]$ is characterized by a three-dimensional network of tetrahedrally linked FeO_4 groups with intercalated $Ba_8Fe(OH)_6^{12+}$ clus-

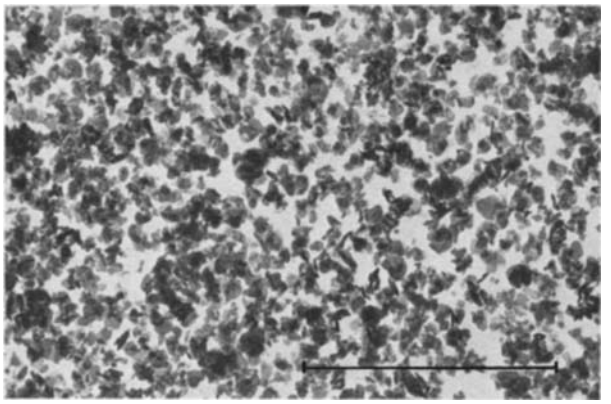

Fig. 12. Hydrothermally produced barium ferrite $BaFe_xO_{19}$ (Fe/Ba = 2.9; NaOH excess = 300 g/L; 170 °C, 8 h) (the distance indicated corresponds to 1 μm).

ters. In contrast $Ba_4[Fe^{III}(OH)_6][Fe^{II}Fe^{III}_7O_{14}]$ exhibits a sheet structure with intercalated Ba^{2+} and $Fe(OH)_6^{3+}$ ions.

In order to suppress corrosive effects, inner vessels of teflon, silver, or platinum have been used, and firmly adhering, pore-free, very thin gold linings produced by explosion plating and applied to the interior wall of the autoclave can also be useful. When silver is used, γ-$AgFeO_2$[179] may also be formed, particularly at high partial pressures of oxygen.

It has been known for some time that ferrites having a spinel-type structure and of composition MFe_2O_4 ($M = Mn^{II}$, Co^{II}, Zn^{II}, Mg^{II}, Fe^{II}, *etc.*) can also be obtained from aqueous solutions at temperatures below 100 °C and under atmospheric pressure. Thus, extremely finely divided isotropic ferrite particles with a spinel-type structure are precipitated when the "neutralization method" or "coprecipitation method" is employed[180, 181], and coarse-grained products of mean particle diameter 0.05 — 1 μm are obtained by the "oxidation method"[182, 183]. However, as shown by our experiments, $BaFe_{12}O_{19}$ cannot be successfully prepared by either method.

5. Prospects

As shown by the example of ferrimagnetic hexagonal barium ferrite, the magnetic properties of a finely divided pigment are determined in the first place by the nature of the bonding, *i.e.* the chemical composition and the crystal structure of the pigment particles. The actual structure of the particles can, in some cases, differ considerably from the ideal crystal structure of the corresponding solid, for example when crystal defects are introduced by milling processes. In addition, the pigment properties are greatly dependent on the state of division of the solid, both the size and shape of the particles and the particle size distribution being of importance. The situation is particularly complicated when the individual pigment particles are not monocrystalline but, in turn, are composed of several monocrystalline regions, and the chemical composition of the monocrystalline regions may differ from those of the grain boundaries.

Finally, the chemistry of the phase boundary solid/binder must also always be taken into account in the development of magnetic pigments in order to achieve, as far as possible, a monodisperse distribution of the pigment particles in the surface-coating, since, when the pigments are used industrially, the physical properties of the information carrier are of decisive importance.

There are therefore two ways of achieving improved or novel pigment properties: on the one hand, chemical preparation of novel solids, and an interdisciplinary investigation of their structural and physico-chemical properties is necessary. On the other hand, methods must be developed by means of which known solids with promising basic properties may be prepared in a pigment form which is optimal for the particular technical requirement. In particular, it is the task of the industrial chemist to work out improved and novel chemical processes and process technologies by means of which the particle geometry and the phase-boundary chemistry may be controlled, and thus the selective adjustment of pigment properties achieved.

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COMMUNICATIONS

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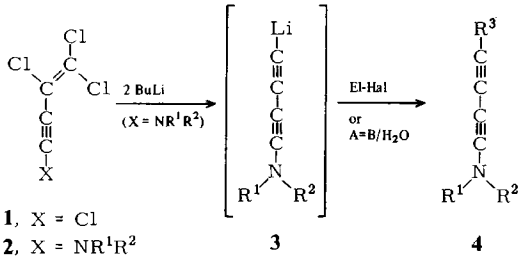
A Simple, Highly Variable Route to (1,3-Diynyl)amines**

By *Gerhard Himbert** and *Michael Feustel*

Until now, (1,3-diynyl)amines have practically only been synthesized by base-catalyzed isomerization of (2,4-pentadiynyl)amines and by bromine-amine exchange on 1-bromo-1,3-alkadiynes[2,4]. Both methods have a relatively limited scope of application and necessitate a multistep synthesis of each (1,3-diynyl)amine.

We have now found a route to the (1,3-diynyl)amine system which, in the penultimate step, permits a large variation in the amine residue (see **1**→**2**), and which, in the last step, allows the introduction of a wide choice of electrophiles and electrophilic π-systems into the 4-position of the diynamine (see **2**→[**3**]→**4**). By use of the corresponding lithium amides we have also extended the synthesis of trichlorovinylynamines **2** *via* the readily accessible perchlorobutenyne **1** (only the *N,N*-dialkyl derivatives *e.g.* **2a** had been known before)[7] to compounds with *aryl*amine groups (see **2b** and **2c**) (Table 1).



1, X = Cl
2, X = NR^1R^2 **3** **4**

Table 1 (Selection). Examples of the prepared compounds **4**. El ≙ electrophile; A=B ≙ >C=O; RNC=O.

2, 3	R^1	R^2	Reagent	4	R^3	Yield [%]
a	$(CH_2)_2O(CH_2)_2$		$ClSiMe_3$	a	$SiMe_3$	43
a	$(CH_2)_2O(CH_2)_2$		$ClSnMe_3$	b	$SnMe_3$	20
b	Me	Ph	H_2O	c	H	54
b	Me	Ph	MeI/HMPT [a]	d	Me	56
b	Me	Ph	$Ph_2C{=}O/H_2O$	e	$C(OH)Ph_2$	70
b	Me	Ph	$BrGePh_3$	f	$GePh_3$	61
b	Me	Ph	$ClSnMe_3$	g	$SnMe_3$	39
b	Me	Ph	$ClPPh_2$	h	PPh_2	50
b	Me	Ph	$ClCO_2Me$ [***]	i	CO_2Me	40
c	Ph	Ph	*t*BuNCO/H_2O	k	C(O)NH*t*Bu	50

[a] Hexamethylphosphoric triamide.

The (3-buten-1-ynyl)amines **2** thus obtained are smoothly converted into the lithium compounds **3** using butyllithium (molar ratio 1:2). These are not isolated, but characterized by transformation into **4**; they can be protonated to **4**, alkylated, hydroxyalkylated, acylated[***], carbamoylated, and transformed into heterosubstituted diynamines. Examples are shown in Table 1.

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[***] Note added during revision: In the meantime—independent of us—acylated diynamines ("push-pull diacetylenes") analogous to **4i** have been synthesized using the same route presented here: U. Stämpfli, M. Neunschwander, *Chimia 35* (1981) 336.

The diynamines **4a–k** are thermally stable, mainly crystalline compounds, which are unaffected by storage. The constitution of the diynamines **4**, which with the exception of **4d**[2] are novel compounds, was verified by exact elemental analyses and spectroscopic data: The very intense IR absorptions in the 2188–2228 cm^{-1} region (often accompanied by bands of medium to low intensity at 2065–2153 cm^{-1}), the appearance of the molecular ion in the mass spectra, and of the signals of the four acetylenic C atoms in the sample ^{13}C-NMR spectra of **4c** and **4i** are characteristic. The reactivity of (1,3-diynyl)amines is, with the exception of some hydrolyses[4], unknown; the additions and cycloadditions of electrophilic molecules which we have studied up till now appear to proceed preferentially at the CC triple bond adjacent to the amino group. In contrast, reaction of the stannylated diynamine **4g** with chlorodiphenylarsane afforded the novel diynamine **4j** ($R^3 = AsPh_2$) *via* exchange of the stannyl group.

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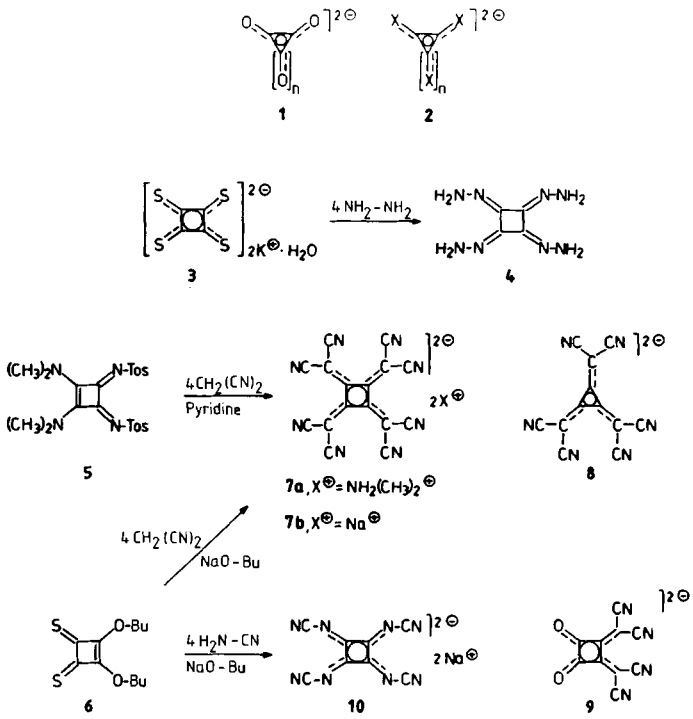
Novel Pseudooxocarbon Dianions of the C_4 Series**

By *Gunther Seitz**, *Rudianto Sutrisno*, *Bernd Gerecht*, *Guido Offermann*, *Roland Schmidt*, and *Werner Massa*

Exchange of the oxygen atoms in oxocarbon dianions **1** by substituents X = S, NR, or =C(CN)$_2$ leads to pseudooxocarbon dianions **2** having similarly delocalized π-electron systems[1]. We have now found that by analogy to the hydrazinolysis of the thiooxocarbon dianion **3** of the C_4 series to give the tetraaza[4]radialene **4**[3], the highly reactive squaric acid derivatives **5** and **6** permit a complete exchange of substituents in only one step with C- or N-nucleophiles. Thereby, novel pseudooxocarbon dianions of the C_4 series such as **7a** and **7b** are formed with malondinitrile and a base, and the first isolable, air-stable salt of the iminocarbon dianion **10**[9a,b] is formed in excellent yield using cyanamide.

The spectroscopic data confirm the high symmetry of these novel aromatic dianions: **7a**: ^{13}C-NMR ([D$_6$]DMSO): δ = 149.6 (four-ring C), 117.6 (CN), 39.7 (*C*—CN), 34.4 (NCH_3); IR (KBr): 2200 (CN), 1440 cm^{-1} (four-membered ring); UV (H_2O): λ_{max} = 484 nm (lgε = 4.69). — **10**: ^{13}C-NMR ([D$_6$]DMSO): δ = 173.2 (four-membered ring C), 117.5 (CN); IR (KBr): 2178 (CN), 1510 cm^{-1}; UV (H_2O): λ_{max} = 376 nm (lgε = 4.6).

A high charge-density on the exocyclic methylene carbon atoms of **7a** is evident from their ^{13}C-NMR shift,



which is comparable to that of the dianion **9**[7] at δ = 38.0; the extreme value of δ = 24.8 for the next lower homologue of **7**, the pseudooxocarbon dianion **8**[8] is, understandably, not reached.

The X-ray structure analysis of **7a** indicates that the point group symmetry of the dianion is only C_2; the two-fold axis lies *in* the plane of the molecule. The dianion is twisted to such an extent that even the four-membered ring is no longer planar (Fig. 1b). Steric hinderance does not

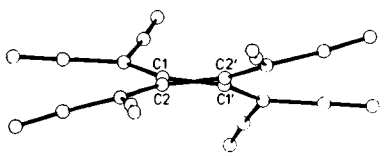


Fig. 1. b) ORTEP representation of the dianion of **7a** in the crystal; view along the two-fold axis.

lead, therefore, to a propeller-like arrangement of the substituents but rather to a tetrahedral distortion. From the bond lengths of the endocyclic [⟨C—C⟩ = 145.3(5) pm] and semicyclic C—C bonds [⟨C—C⟩ = 138.7(9) pm], a π-bond character typical of pseudooxocarbon dianions comparable to that of squarates or tetrathiosquarates, can be derived[1].

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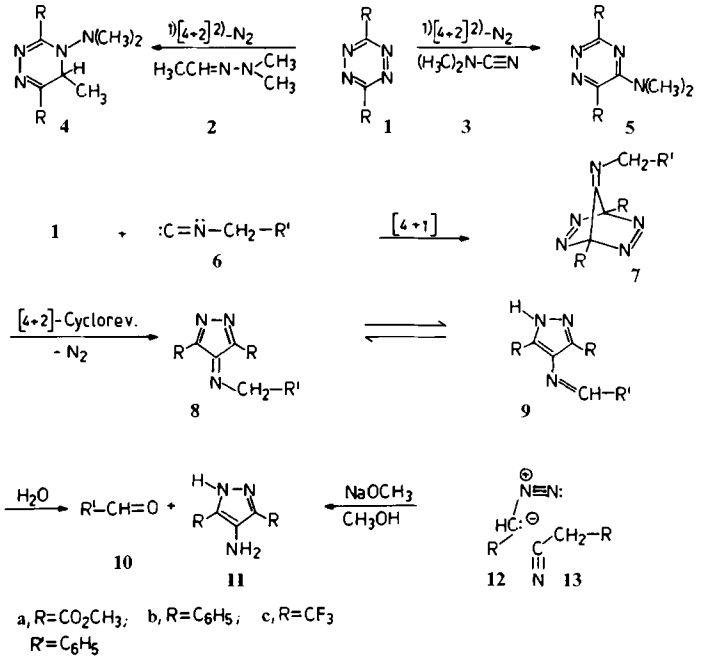
[4+1]Cycloaddition of Isocyanides to 1,2,4,5-Tetrazines: A Novel Synthesis of Pyrazole

By *Peter Imming, Rolf Mohr, Eric Müller, Wolfgang Overheu,* and *Gunther Seitz**

The high reactivity of 1,2,4,5-tetrazines **1** relative to donor-substituted CN multiple bonds[1] such as in the hydrazones **2** or cyanamides **3** makes amine-substituted triazines **4** and **5** respectively, surprisingly readily accessible by Diels-Alder addition with inverse electron demand[2]. We have found that the C=N functionality in isocyanides **6** behaves differently: the reaction of **1a—c** with benzyl isocyanide **6** is the first example of a synthesis in which five-membered heterocycles result from a [4+1]cycloaddition and subsequent [4+2]cycloreversion.



In the initial step, the previously only rarely achieved[3] [4+1]cycloaddition of **6** to **1**, in which the azine system is *s-cis*-fixed, should dominate over a [4+2]cycloaddition. The non-isolable tetraazanorbornadienimine derivative **7**, whose high angular strain causes elimination of nitrogen *via* a [4+2]cycloreversion[4] in a rapid subsequent reaction, is formed; the resulting energy-rich diazacyclopentadienonimine derivative **8** rapidly tautomerizes to the aromatic pyrazole **9**. Hydrolysis of **9a—c** leads quantitatively to the pharmacologically interesting aminopyrazoles **11a—c**. The structures of **11a** and **11b** were confirmed by independent synthesis[5]. Hence, *e.g.*, condensation of **12a** and **13a** also led, after transesterification to **11a**, although in considerably lower yield.

Procedure

9a—c: 1a—c (5 mmol) is dissolved in 20 mL of anhydrous dichloromethane, and a solution of **6** (5 mmol) in 10 mL of dichloromethane added dropwise at *ca.* 0 °C; the mixture is left to react until the red color of **1** has disappeared. **9a** (m.p. = 161 °C, ethyl acetate, yield 65%) as well as **9c** (m.p. = 180—181 °C, carbon tetrachloride, yield 75%) are obtained after concentration; crystals of **9b** (m.p. = 220 °C, ethyl acetate, yield 70%) precipitate out after a short time.

11a, b: 9a is completely hydrolyzed to **11a** (m.p. = 185 °C, ethyl acetate, yield 95%) by addition of water. **9b** is hydrolyzed by heating for a short time in conc. hydrochloric acid. Treatment of the hydrochloride with an aqueous solution of potassium carbonate led quantitatively to **11b** (m.p. = 208 °C, ethanol).—**9** and **11** gave correct C,H,N analysis results and appropriate spectra (MS, IR, ^{1}H-NMR).

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A Novel Anionic Five-Coordinate Tris(trichlorostannato)platinum(II) Complex**

By *Alberto Albinati, Ralph Nägeli, Heinz Rüegger,* and *Paul S. Pregosin**

Trichlorostannato complexes of platinum(II) are recognized as useful hydrogenation and hydroformylation catalysts[1]. Although the exact composition of the active species is not clear, it is known that the catalyst functions optimally when the ratio Sn : Pt exceeds five, and therefore poly(trichlorostannato) derivatives may be important intermediates. We have recently shown that mono- and bis(trichlorostannato)platinum(II) complexes containing either tertiary phosphane or arsane ligands are stable in solution[4,6], and now report the synthesis and characterization of the anion

$[Pt(SnCl_3)_3(AsMe_3)_2]^{\ominus}$ **1**

which was isolated as its bis(triphenylphosphorandiyl)ammonium salt ($N(PPh_3)_2^{\oplus}$, PPN).

The PPN salt of **1** and its $AsEt_3$ analog **2** are readily prepared by the reaction of *cis*-$[PtCl_2L_2]$ with $SnCl_2$ (molar ratio 1 : 3) in acetone. Pertinent NMR data for the PPN salt of **1** ($CDCl_3$, −40 °C) are: $\delta(^{119}Sn) = -67$, $\delta(^{195}Pt) = -5364$, $\delta(^{13}C) = 19.7$, $^1J(^{195}Pt,^{119}Sn) = 19037$ Hz, $^2J(^{119}Sn,^{117}Sn) = 17504$ Hz; PPN salt of **2** ([D_6]acetone, −70 °C): $\delta(^{119}Sn) = -79$, $\delta(^{195}Pt) = -5400$, $^1J(^{195}Pt,^{119}Sn) = 19788$ Hz, $^2J(^{119}Sn,^{117}Sn) = 18115$ Hz.

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Interestingly, in the related $[Pt(SnCl_3)_3(PEt_3)_2]^{\ominus}$, which we assume has the same structure as **1**, $^1J(^{195}Pt,^{31}P)$ is only 1460 Hz. The Pt- and Sn-NMR parameters are similar to those for **1** and **2**. This $^1J(^{195}Pt,^{31}P)$ value is quite modest when compared to the values of 2400–2600 Hz often found in *trans*-$[PtCl_2(PR_3)_2]$ complexes and still much smaller than the value 2014 Hz found in the five-coordinate tetradentate chelate complex $[Pt(SnCl_3)\{P(o\text{-}AsPh_2C_6H_4)_3\}]$ in which P and Sn occupy pseudoaxial positions. This suggests a relatively weak Pt—P bond in the anion $[Pt(SnCl_3)_3(PEt_3)_2]^{\ominus}$.

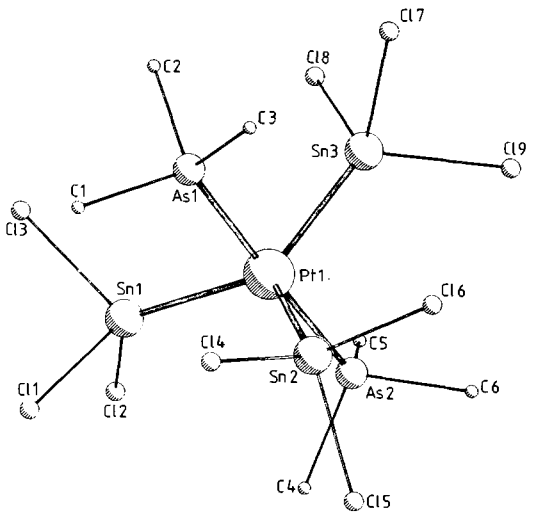

Fig. 1. Structure of anion **1** in crystals of the PPN salt of **1**. Bond lengths [pm]: PtAs1 244.5(2), PtAs2 242.7(2), PtSn1 261.2(1), PtSn2 261.4(2), PtSn3 257.9(1), SnCl 238.0±1.0(7) (average value).—Bond angles [°]: As1PtAs2 177.7(6), Sn1PtSn2 117.1(4), Sn1PtSn3 122.9(4), Sn2PtSn3 119.9(5), As1PtSn1 88.6(1), As1PtSn2 90.7(1), As1PtSn3 88.4(1), As2PtSn1 92.5(1), As2PtSn2 90.6(1), As2PtSn3 89.2(1).

The coordination geometry around the Pt atom in **1** (Fig. 1) is distorted trigonal bipyramidal, with the $AsMe_3$ ligands in axial positions. The average PtSn bond length is 260.2±2.0(1) pm. This is slightly larger than the average equatorial PtSn bond lengths in $[Pt(SnCl_3)_5]^{3\ominus}$ **3** (257.2)[10], but considerably longer than the PtSn bond in $[PtCl(SnCl_3)(PhC(NH_2)=NOH)(PEt_3)]$ **4** (250.1)[11]. The average PtAs distance in **1** is also quite long (243.6±1.3(2) pm) relative to that in the complexes *sym-trans*-$[Pt_2Cl_4(AsMe_3)_2]$ (230.8) and *trans*-$[PtCl_2N(CH_3)=CH-(p\text{-}CH_3C_6H_4)(AsEt_3)]$ (234.6). The SnCl bonds in **1** average 238.0±1.0(7) pm and are in good agreement with the value of 237.2 pm found for the equatorial $SnCl_3$ ligands in **3**, but longer than the SnCl bonds in **4** (234.0).

Given the rather long PtSn and PtAs bond lengths in **1** and the small coupling constant $^1J(^{195}Pt,^{31}P)$ for the PEt_3 complex, ligand dissociation is not unexpected. It is probable but not certain that an $SnCl_3^{\ominus}$ ligand leaves the coordination sphere of Pt to produce the known $[Pt(SnCl_3)_2L_2]$ complex.

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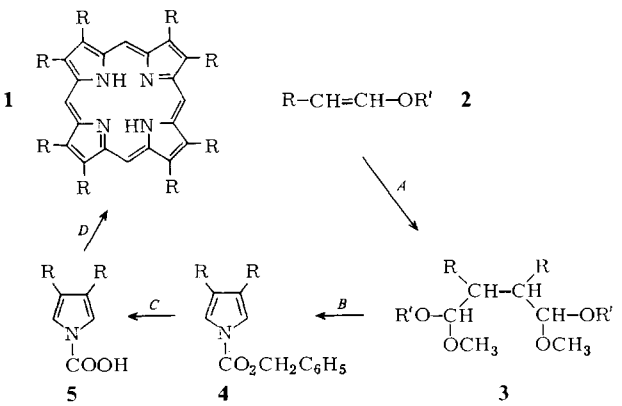
Novel Synthesis of Octaalkyl- and Octaisoalkylporphyrins

By *Henry Jacques Callot**, *Abderrazak Louati*, and *Maurice Gross*

Octaalkylporphyrins and particularly octaethylporphyrin **1a** are the simplest and most useful models for natural porphyrins, and are accessible through multistep syntheses[1]. We have now found an alternative reaction sequence (Scheme 1) which takes advantage of the symmetry of the products and their precursors, and which permits for the first time, the synthesis of an octaisoalkylporphyrin, the isopropyl derivative **1c**.



Scheme 1 (Section). Synthesis of octaalkylporphyrins **1a** and **1b** and octaisoalkylporphyrin **1c** [**a**, R=C_2H_5; **b**, R=*n*-C_4H_9; **c**, R=$CH(CH_3)_2$]. *A*: anodic oxidation in methanol/$NaClO_4$/2,6-lutidine; *B*: benzyl carbamate in acetic acid (isolation of **3** not necessary); *C*: H_2/Pd in methanol; *D*: formaldehyde/O_2/acetic acid/pyridine. R'=C_2H_5.

Anodic oxidation[2] of alkenyl alkyl ethers **2a–c** gave acetals **3a–c**, which were cyclized to afford pyrroles **4a–c** using benzyl carbamate in acetic acid [**4a**, yield 27%, m.p. <20 °C, ^{1}H-NMR ($CDCl_3$): δ=1.15 (t; 6H), 2.36 (q, 4H), 5.28 (s, 2H), 6.99 (s, 2H), 7.35 (s, 5H)]. The unstable acids **5a–c** obtained by removal of the protecting groups react with formaldehyde in presence of air[3] to furnish octaethyl- **1a**, octabutyl- **1b**, and octaisopropylporphyrin **1c** (yields relative to **4**: 52, 35, and 43%, respectively).

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One-Pot Synthesis of 1-Alken-5-yne Derivatives[1]

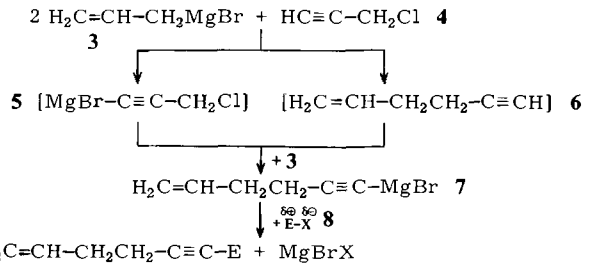
By *Hanno Priebe* and *Henning Hopf**

Propargyl halides **1** metalated in the 3-position are equivalent to the zwitterion **2**, a species suitable for use as a functionalized C_3-synthon for the synthesis of complicated carbon frameworks since it should couple with both electrophilic and nucleophilic substrates:

1 $M-C\equiv C-CH_2-Hal \triangleq {}^{\ominus}C\equiv C-CH_2^{\oplus}$ **2**

As shown by the following one-pot reaction for the synthesis of 1-alken-5-yne derivatives **9**, this is indeed the case even if the reactive centers in **1** are not activated simultaneously, but successively. The compounds (see [2]) can be readily prepared if *two* equivalents of allylmagnesium bromide **3**[3] react first with propargyl chloride **4**[4].

Thereby 5-hexen-1-ynylmagnesium bromide **7** is formed in almost quantitative yield *via* **5** (type **1/2**) or **6**; **7** reacts with electrophilic reagents **8** to give the desired products **9**[5].



E—X **8**	—E in **9**	Yield [%]
H_2O	—H	93
CH_2O	$-CH_2OH$	18
CH_3CHO	$-CH(OH)CH_3$	50
C_2H_5CHO	$-CH(OH)C_2H_5$	32
$(CH_3)_2CH-CHO$	$-CH(OH)-CH(CH_3)_2$	45
$H_2C=CH-CHO$	$-CH(OH)-CH=CH_2$	31
$(CH_3)_2C=O$	$-C(OH)(CH_3)_2$	83
$(CH_2)_4C=O$	$-C(OH)(CH_2)_4$	35
$H_2C=CH-CO-CH_3$	$-C(OH)CH_3(CH=CH_2)$	22
$(CH_3)_2N-CHO$	—CHO	15
$(CH_3CO)_2O$	$-CO-CH_3$	17
CO_2	$-CO_2H$	63
$(CH_2)_2O$	$-CH_2CH_2-OH$	13

A first impression of the scope of application of the method is given by the tabular summary of reactions, whose yields except for the reaction of **7** with acetone have not been optimized. The Grignard reagent **3** and the coupling component **4** can be varied: for example, ethylmagnesium bromide, **4**, and acetaldehyde produce 3-heptyn-2-ol (22%)[5]; 7-octen-3-yn-2,5-diol (36%) is formed from **3**, propionaldehyde, and acetyldehyde.

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[4] The use of propargyl *chloride* **4** is decisive, since **4**, in contrast to the corresponding bromide, does not react with the excess magnesium present in ether.
[5] All the new compounds were characterized by the usual spectroscopic methods and by elemental analysis.

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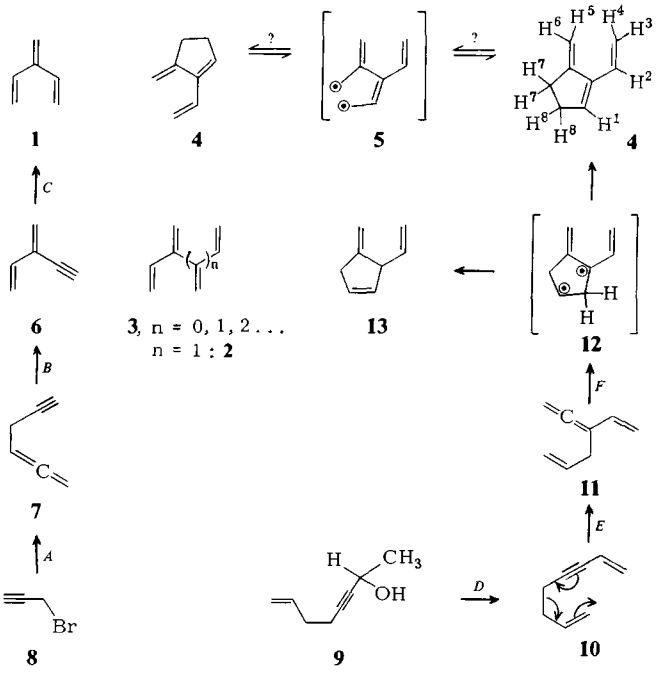
Cross-Conjugated Trienes by Thermal Isomerization of Alkynes[1]

By *Hanno Priebe* and *Henning Hopf**

Although simple cross-conjugated polyolefins such as 2-vinyl-1,3-butadiene **1** and 3,4-bis(methylene)-1,5-hexadiene **2** (≡ **3**, n = 1) have been known for some time, the homologous series of hydrocarbons **3** ("dendralenes") beginning with these substances has been neglected until now[5].

For the synthesis of dendralenes, classical reactions such as eliminations and condensations[5] are preferred. In addition to a novel route to **1**, we also report the synthesis of the conformationally partially fixed 2-vinylbutadiene **4**. Both syntheses are related to each other in the sense that the educts already contain the desired number of π-electrons and carbon atoms. Compound **4** is of interest for the investigation of a novel degenerate 8π-isomerization (automerization) *via* diradical **5**.



A: 1. Mg/ether, 2. CuCl, 3. + **8** (60% total yield); *B*: 500 °C, 49%; *C*: Lindlar-H_2, 60%; *D*: TsOH, 120–150 °C/100 torr, 24%; *E*: 400–500 °C; *F*: 440 °C. ^{1}H-NMR data for **4** ($CDCl_3$): $\delta = 2.43$ (m; $2H^8$), 2.64 (m, $2H^7$), 4.84 (m, H^6), 4.99 (dtt, H^5, $J_{57} = 2.6$, $J_{58} = 1.1$ Hz), 5.17 (dm, H^4), 5.53 (dm, H^3), 6.21 (ps, H^2), 6.39 (dddt, H^1, $J_{13} = 17.6$, $J_{14} = 11.1$, $J_{18} = 0.8$, $J_{12} = 1.1$ Hz).

For the preparation of **1**, propargyl bromide **8** is dimerized to 1,2-hexadien-5-yne **7**, which is subsequently isomerized at 500 °C to 2-ethynyl-1,3-butadiene **6**; Lindlar hydrogenation of **6** then affords **1**[5].

The starting material for **4** is 1,7-octadien-3-yne **10**, which is obtained from the alkenynyl alcohol **9**[9] by acid

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catalyzed dehydration. **10** isomerizes to the allene **11** *via* a Cope rearrangement (400—500 °C). As expected[10] **11** reacts to give the diradical **12**, which stabilizes itself by a 1,2-hydrogen shift to yield **4** and its nonconjugated isomer **13**. Whereas at 440 °C, 44% **4** and 52% **13** are produced (rest **10** and **11**, GC), **13** is practically the only rearrangement product at 500 °C (93%, rest **4**).

The structural assignments for **4** are based on ^{1}H- and ^{13}C-NMR data, as well as on vibrational- and electronic-spectra [acetonitrile, $\lambda_{max} = 252$ nm ($\log\varepsilon = 3.7$)]. In comparison to the conformationally less restricted **1** [$\lambda_{max} = 224$ nm ($\log\varepsilon = 4.4$)], **4** exhibits a bathochromic shift which almost corresponds to that of the completely fixed 3-methylene-1,4-cyclohexadiene [$\lambda_{max} = 242$, sh at 247 nm ($\log\varepsilon = 4.4$[12])].

Pyrolyses of methyl derivatives of **10** result in the corresponding derivatives of **4** and **13**. Moreover, since a further cross-conjugated triene (1,2-dihydropentalene) can be synthesized by thermal rearrangement of 1,2-diethynylcyclobutane, the thermal rearrangement of alkynes promises to become a useful method of preparing branched polyolefins.

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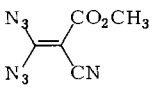
Geminal Vinyl Diazides: Potential Precursors of Functionalized Alkylidenecarbenes; Synthesis and Reactions of 3,3-Diazido-2-cyanoacrylic Acid Methyl Ester**

By *Robert Carrié, Daniel Danion, Erich Ackermann,* and *Rolf W. Saalfrank**

So far very little is known about heterosubstituted[4] or functionalized[5] unsaturated carbenes. We have now investigated 3,3-diazido-2-cyanoacrylic acid methyl ester **6** as potential precursor of cyano(methoxycarbonyl)vinylidene **13**.

A solution of 0.5 g of 3,3-dichloro-2-cyanoacrylic acid methyl ester[9] in a small amount of acetone is added at −15 °C to an excess of sodium azide dissolved in acetone/water (1 : 1). After a few seconds spectroscopically pure, pale yellow-green crystals of the ester **6** precipitate from the solution [UV (CH_3OH): $\lambda_{max} = 304$, 244 nm ($\lg\varepsilon = 4.34$, 4.10)].



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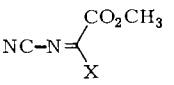
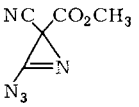


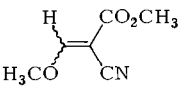
7, X = OCH_3
10, X = CN



9

On addition to methanol at just below the boiling point **6** decomposes with vigorous evolution of N_2; subsequent removal of methanol and recrystallization of the residue from diethyl ether afford colorless crystalline 2-(*N*-cyanimino)-2-methoxyacetic acid methyl ester **7** [yield 75%; m.p. 54 °C; ^{1}H-NMR ($CDCl_3$): $\delta = 3.96$, 4.00 (s, 6H, CH_3); ^{13}C-NMR ($CDCl_3$): $\delta = 54.36$, 57.94 (q, CH_3; $^1J_{CH} = 150$ Hz), 110.23 (s, CN), 155.38, 164.57 (q, C=N— and C=O resp., $^3J_{CH} = 4$ Hz].

We assume that on heating, **6** initially undergoes a 3,5-ring-closure with N_2-elimination[13]. The resulting azidoazirine **9** then undergoes further loss of N_2 and rearrangement to form the ester **10**[15], which, on addition of methanol and elimination of hydrogen cyanide affords **7**. The intermediate **10** can be trapped with 2,3-dimethylbutadiene to give a tetrahydropyridine derivative *via* a Diels-Alder reaction.



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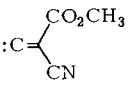

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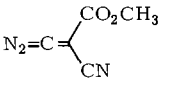

16

Irradiation (3 h, Original Hanau, high-pressure radiation lamp TQ 150) of **6** in methanol at −30 °C affords **7** (70%) together with the photoproduct **12** (30%).

The 2-cyano-3-methoxyacrylic acid methyl ester **12** probably results from an insertion of the intermediate alkylidenecarbene **13** into the H—O bond of methanol. It is still unclear, however, which other intermediates are involved in the formation of **13**. A further possible route to the vinyl ether **12** is the addition of methanol to the diazoethene **16**[6] to give the corresponding vinyldiazonium methoxide, followed by decomposition.

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[**] Geminal Vinyl Diazides, Part 1 (Part of a Dissertation by *E. A.* (1981)). This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. *R. W. S.* thanks the University of Rennes for a visiting Professorship.

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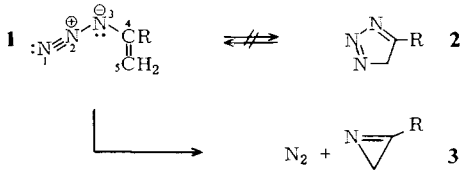
Substituent-Dependent Competition between 1,5- and 3,5-Cyclization in Vinyl Azides; 4*H*-Triazoles from 3,3-Diazido-2-cyanoacrylic Acid Methyl Ester and Primary Amines**

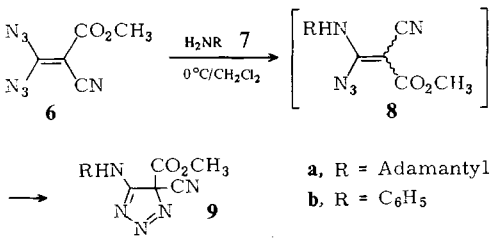
By *Robert Carrié, Daniel Danion, Erich Ackermann,* and *Rolf W. Saalfrank**

Vinyl azides **1** do not generally cyclize to 4*H*-triazoles **2**. Instead, they eliminate N_2 and yield 2*H*-azirines **3**[1,2]. For formation of **3**, a 3,5-ring-closure of **1** with simultaneous N_2-elimination (no free nitrene) is favored.



Introduction of an electron donor into position 4 of **1** leads to increased nucleophilicity at C-5 and lowers the rotation barrier of the CC double bond. Hence, a 1,5-ring-closure should be possible, to give the 4*H*-triazole.

Reaction of 3,3-diazido-2-cyanoacrylic acid methyl ester **6** with amines **7** in dichloromethane at 0 °C leads to the 4*H*-triazoles **9**. We assume that **6** reacts with the amines by nucleophilic substitution to give the donor-substituted vinyl azides **8**, which spontaneously cyclize to **9**[3] [**9a**, yield 60%; m.p. 121 °C (dec.); ^{1}H-NMR ($CDCl_3$): $\delta = 1.66-2.03$ (m, 15 adamantyl-H), 3.73 (s, 3H, CH_3), 9.35 (s, 1H, NH); **9b**, yield 61%; m.p. 84 °C (dec.); ^{1}H-NMR ($CDCl_3$): $\delta = 3.66$ (s, 3H, CH_3), 7.22 (m, 5H, C_6H_5), 10.96 (s, 1H, NH)].



a, R = Adamantyl
b, R = C_6H_5

At 35 °C, **6** reacts completely differently: It rapidly decomposes on heating; double N_2-elimination and rearrangement lead initially to 2-cyano-2-(*N*-cyanimino)acetic acid methyl ester[4], which on addition of aniline or 1-naphthylamine and elimination of hydrogen cyanide affords *N*-aryl-2-(*N*-cyanimino)glycine methyl ester.

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[**] Geminal Vinyl Azides, Part 2 (Part of a Dissertation by *E. A.* (1981)). This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. *R. W. S.* thanks the University of Rennes for a visiting Professorship. - Part 1: [4].

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Orbital Symmetry Analysis of Triplet-Singlet Spin-Flip during Thermal Isomerization of Tetrahedral to Planar Nickel(II) Complexes**

By *E. Amitai Halevi** and *Rudolf Knorr**

Ni^{II} ($3d^8$) may form (pseudo)tetrahedral, paramagnetic or planar, diamagnetic complexes, whose mutual interconversion requires a spin change of $\Delta S = 1$. Although this might, therefore, be expected to be a slow process, numerous examples[1,2] of such triplet-singlet interconversions have been reported to be immeasurably fast, and in only a few cases could the two species be resolved, or stable enantiomers be detected by ^{1}H-NMR spectroscopy.

We have studied this isomerization by means of Orbital Correspondence Analysis with Maximum Symmetry (OCAMS)[20b,c], extended to reactions which do not conserve spin-multiplicity[21] and with consideration of reduction of symmetry along degenerate displacement coordinates[22a].

The reaction starts by a nuclear displacement belonging to the representation E of the tetrahedral symmetry point group, T_d. Choosing the three equivalent C_2-axes as the Cartesian axes and focusing attention on the z-axis, the two degenerate modes of E-symmetry can be described[22a] as z-compression (S_a) and "z-twist" (S_b) (Fig. 1).

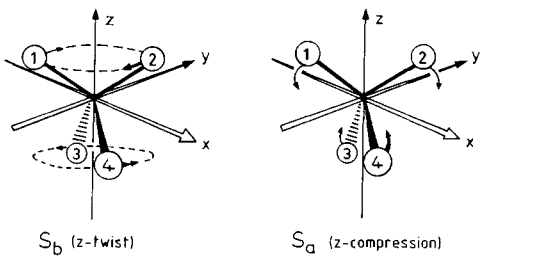

Fig. 1. The two degenerate (e) deformations of a tetrahedral molecule.

The correspondence diagrams for the two pathways are set up in Fig. 2. The *kernel* symmetry, D_2, is either achieved directly by twisting the tetrahedral complex along S_b, or stepwise: $T_d \rightarrow D_{2d}^z \rightarrow D_2$. The first step, S_a^{-1}, in which the angles between ligands ① and ② and between ③ and ④ *decrease* towards 90°, corresponds to chelation. The twist of the resulting bischelate leads to D_{2h} symmetry, and fur-

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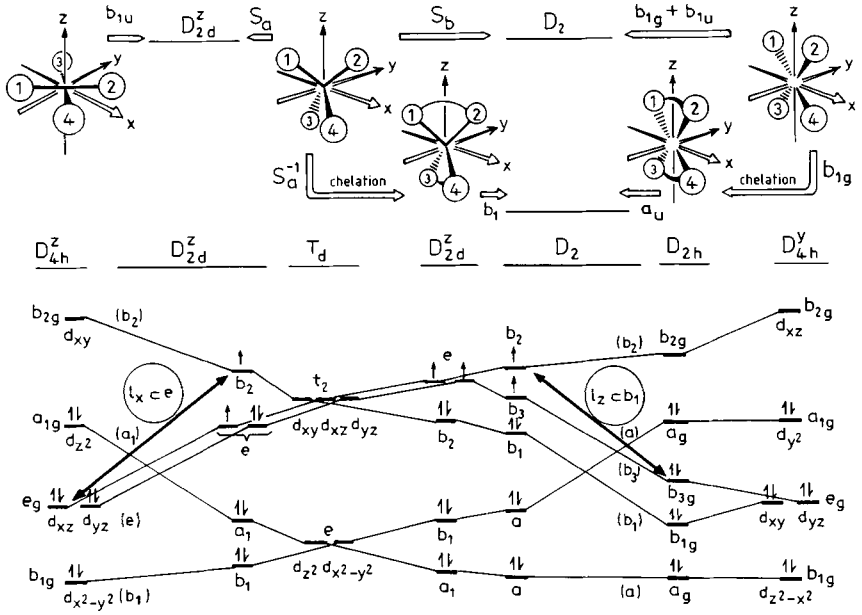

Fig. 2. Correspondence diagrams for tetrahedral to planar isomerization of nickel(II) complexes. Left: along compression coordinate (S_a). Right: along twist coordinate (S_b), with or without chelation (see text).

ther dechelation to the D^y_{4h} point group. Twisting the planar complex in the opposite direction can also be accomplished in two steps. Thus, the correspondence diagram for the S_b pathway is $T_d \rightleftharpoons (D^z_{2d}) \rightleftharpoons D_2 \rightleftharpoons (D_{2h}) \rightleftharpoons D^y_{4h}$. For a nonchelated complex, the group labels enclosed in parentheses can be regarded as "virtual symmetries".

Following the twist pathway S_b we see that three of the doubly-occupied 3d orbitals in the planar complex correspond directly in D_2 with the three doubly-occupied orbitals of the tetrahedral complex. The fourth, d_{yz}, corresponds directly with one of the singly-occupied b_3 orbitals, whereas the other (b_2) corresponds with the empty d_{xz} orbital (b_{2g}). If the ground state of the (pseudo)tetrahedral complex were a *singlet* of the same electron configuration (*i.e.* open shell), OCAMS[20b] would prescribe an *induced* correspondence between $d_{xz}(b_2)$ and $d_{yz}(b_3)$ in order to allow transfer of an electron from one to the other. However, the requisite nuclear displacement along a b_1 coordinate implies the excitation of at least one of the high-energy t_2 vibrational modes of the tetrahedral molecule, which would raise the activation energy of the spin-conservative isomerization, thus rendering it "disallowed".

Since the transfer of an electron between d_{xz} of the tetrahedral triplet and d_{yz} of the planar singlet is accompanied by spin-flip, the b_1 perturbation of symmetry need not be limited to vibrations, but can be a *circulation of charge* in the xy-plane, which generates a magnetic moment about the z-axis and allows formation or annihilation of the z-component of the spin triplet with conservation of total (orbital *plus* spin) angular momentum[21]. Isomerization with spin-flip is "allowed" along the S_b pathway for chelated and nonchelated complexes alike, in the sense that a spin-orbit coupling component exists which has the proper symmetry (b_1 of D_2) to permit the spin-flip to occur.

The compression pathway (S_a) is also "allowed", but—of course—only for nonchelated complexes: as the tetrahedral triplet distorts slightly to D^z_{2d}, the ^3E state, with one electron in b_2 and the other in e, is stabilized. The perturbation required to induce one-electron correspondence between a b_2 and an e orbital would be of symmetry species e. Transfer of an electron from d_{xy} to one of the degenerate e orbitals (d_{xz} or d_{yz}) can be induced by rotation of charge about x or y (also of symmetry species e), annihilating the spin of the x or y component of the triplet[21] and producing the square planar singlet.

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Synthesis and Properties of *N*-[1-(Arylcarbonyloxy)alkyl]pyridinium Salts**

By *Ernst Anders** and *Thomas Gassner*

Little is known about the reaction of carbonyl compounds with acyl chlorides in pyridine. Ketones such as acetophenone react only slowly with benzoyl chloride in pyridine to give, particularly, 4-substituted 1-acyl-1,4-dihydropyridines, as well as tar-like by-products in low yield[1]. Addition products of some aldehydes have not been more thoroughly described[2]. We found that the *N*-[1-(arylcarbonyloxy)alkyl]pyridinium chlorides **4** are formed at room temperature in 75—90% yield from aldehydes **3** and arene carboxylic acid chlorides (*e.g.*: **4b**, $R^1 = R^2 = C_6H_5$, m.p. = 169 °C, ν(CO) = 1740 cm^{-1}; **4d**, $R^1 = C_6H_5$, $R^2 = n$-

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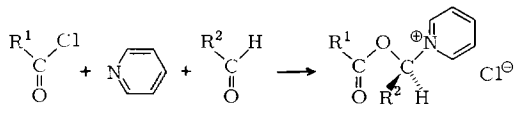


(a)

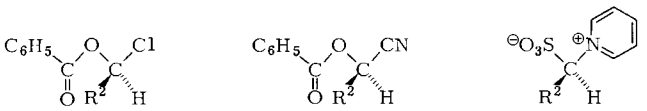
1 2 3 4

R^1 = Aryl; R^2 = Aryl, Alkyl

C_3H_7, m.p. = 90 °C, ν(CO) = 1730 cm^{-1}). Some of the chlorides **4** are hygroscopic, and frequently can only be prepared in analytically pure form with one mol of water of crystallization. The salts of **4** with BF_4^-, $SbCl_6^-$, and FSO_3^- instead of Cl^-, do not have this property, and can be readily prepared from the chlorides **4**.

The salts **4** can be stored for several months at room temperature, and are readily soluble and stable in aqueous hydrochloric acid. In aqueous alkali (even at room temperature in aqueous $NaHCO_3$) they decompose to the starting materials; the aldehydes **3** can be reisolated in good yield. Secondary reactions of the aldehydes were not observed. Reaction (a) therefore offers a straightforward method of protecting the aldehyde group against attack by acids.

At higher temperature the exchange of the pyridine ring in **4** ($R^1 = C_6H_5$) by chloride ion occurred; the corresponding α-chlorobenzyl benzoates **5a**[6] are distilled out *in vacuo*

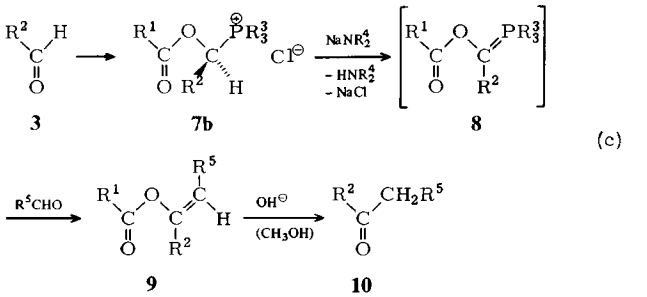


5a, R^2 = C_6H_5 **5b**, R^2 = Aryl, Alkyl **6**, R^2 = Aryl

from the reaction mixture. *O*-acylated cyanohydrins **5b** can be prepared under particularly mild conditions (25 °C, water) using KCN, and the novel betaines **6** can be synthesized with $KCN/NaHSO_3$.

With tributyl- or triphenylphosphane[9], instead of pyridine [eq. (a)] we obtained the phosphonium salts **7**, which have not been specifically studied before (**7a**, $R^1 = p$-$CH_3OC_6H_4$, $R^2 = p$-$CH_3C_6H_4$, $R^3 = n$-C_4H_9, ν(CO) = 1730 cm^{-1}; **7b**, $R^1 = R^2 = R^3 = C_6H_5$, ν(CO) = 1740 cm^{-1}). For example, **7a** reacts with cyanide to give an analogue of **5b**.

These salts **7** derived from aldehydes can be deprotonated under mild conditions (**7b** *e.g.* at −55 °C in tetrahydrofuran) using sodium bis(trimethylsilyl)amide to give the phosphorane **8**. **8** *in situ* with aldehydes reacts immediately to give the enol ester **9**, which as expected readily undergoes saponification to afford the ketone **10**. The reaction



(c)

3 7b 8 9 10

$R^1 = R^2 = R^3 = C_6H_5$; $R^4 = Si(CH_3)_3$; $R^5 = p$-$O_2NC_6H_4$

sequence (c), therefore, affords a novel, facile method to bring about an umpolung[12] of the carbonyl carbon atom in aldehydes.

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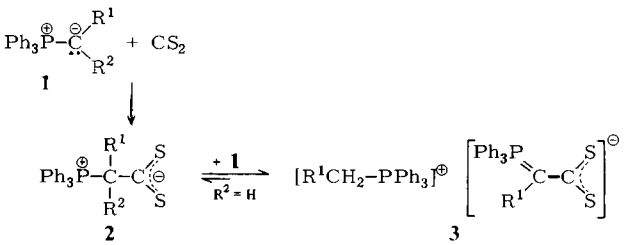
2-Methyl-2-triphenylphosphoniodithiopropionate—A Photosensitive Complex Ligand with Labile P—C Bond**

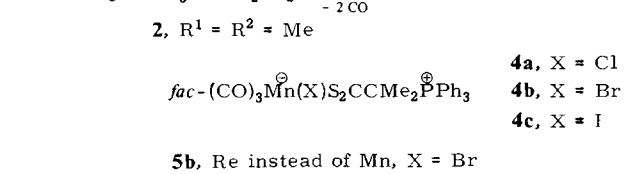
By *Udo Kunze**, *Reinhard Merkel*, and *Werner Winter*

Alkylidenephosphoranes attack heteroallenes nucleophilically[1]. Until now, nothing was known about the complex chemical properties of the initially formed betaines. With carbon disulfide only the disubstituted ylides **1** give stable betaines **2**[4,5]; ylides **1**, R^1 and/or $R^2 = H$, usually react spontaneously to yield phosphonium salts **3**[4].



1 2 3

Reaction of **2**, $R^1 = R^2 = CH_3$, with pentacarbonylmanganese halides (molar ratio 1 : 1 in tetrahydrofuran, 1—3 d stirring) under conditions of strict exclusion of light produces the violet tricarbonyl complexes **4a—c** (*ca.* 75%



2, $R^1 = R^2 = Me$

fac-$(CO)_3Mn(X)S_2CCMe_2PPh_3$ **4a**, X = Cl **4b**, X = Br **4c**, X = I

5b, Re instead of Mn, X = Br

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[+] X-ray structure analysis.

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yield) which are extremely light sensitive in solution and spontaneously decompose when irradiated with a laser (Krypton laser, 647.1 nm, 1 W).

In the carbonyl region, each of the novel complexes **4a–c** exhibits three intense IR absorptions of almost the same frequency, which correspond to a facial arrangement of the carbonyl groups. The analogous rhenium complex **5b** can be prepared from $BrRe(CO)_5$ or, better, from $[BrRe(CO)_4]_2$. The small shifts in the ^{1}H- and ^{31}P-NMR spectra upon coordination indicate similar bonding patterns in the free and coordinated betaine ligands **2**.

In the reaction of the phosphonium salts **3**, $R^1 = CH_3$ or H, with $BrMn(CO)_5$ and $BrRe(CO)_5$, the expected *cis*-tetracarbonyl complexes with anionic ligands (anion of **3**) were detected by IR spectroscopy, but could not be isolated. The more stable cyano(phosphorandiyl)dithioacetato complex, the first example of this structural type, was obtained from **2**, $R^1 = CN$, $R^2 = H$[7].

In order to confirm **4a–c** and **5b** as zwitterionic neutral complexes, X-ray crystallographic structure determinations were performed (Fig. 1). Both complexes crystallize isomorphically in the space group $P2_1/c$, but they decompose at room temperature in the X-ray beam. The reflection data were therefore collected at $-110\,^\circ C$ (no reduction in intensity).

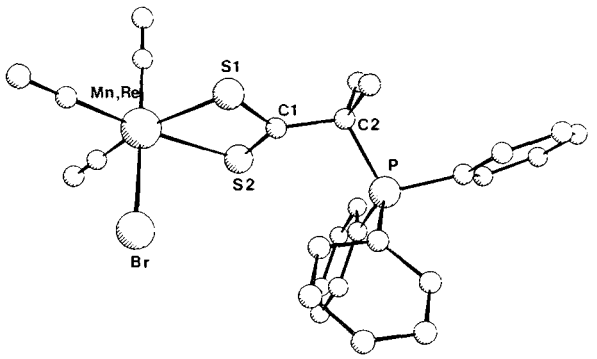

Fig. 1. Molecular structure of **4b** and **5b** at $-110\,^\circ C$ in the crystal. Important distances and angles of **4b**: Mn—S1 2.351(1), Mn—S2 2.380(1), S1—C1 1.691(5), S2—C1 1.675(5), C1—C2 1.522(6), P—C2 1.863(5) Å; S1—C1—S2 112.5(3)°; **5b**: Re—S1 2.488(1), Re—S2 2.503(1), S1—C1 1.717(4), S2—C1 1.664(4), C1—C2 1.526(5), P—C2 1.876(4) Å; S1—C1—S2 113.6(2)°.

The decomposition of the crystals at room temperature upon irradiation presumably results from rupture of the P—C2 bond, *i.e.* from cleavage of PPh_3. Data were measured for both compounds at room temperature (10–20% reduction in intensity within 2–3 d, $R = 0.07-0.10$); the "average" structures obtained from these data clearly show the "drift" of the PPh_3 groups with P—C2 distances of *ca.* 2.0 Å!

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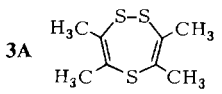
Formation of Bis(isopropylidene)-1,2,4-trithiolane from 2-Methyl-2-triphenylphosphoniodithiopropionate**

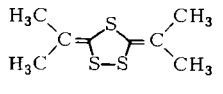
By *Udo Kunze**, *Reinhard Merkel*, and *Werner Winter*

2-Methyl-2-triphenylphosphoniodithiopropionate **1** only reacts with carbonylmanganese and -rhenium halides under strict exclusion of light to afford exclusively *fac*-tricarbonyl complexes **2**[1].

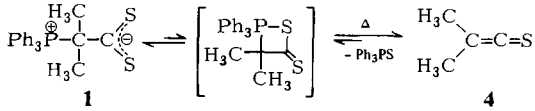
$$BrM(CO)_5 + \underset{\mathbf{1}}{Ph_3\overset{\oplus}{P}CMe_2CS_2^{\ominus}} \xrightarrow[-2CO]{THF,\ 25\,^\circ C} \underset{\mathbf{2},\ M = Mn,\ Re}{fac\text{-}(CO)_3\overset{\ominus}{M}(Br)S_2CCMe_2\overset{\oplus}{P}Ph_3}$$

Reaction of **1** with $BrRe(CO)_5$ in boiling tetrahydrofuran (THF) under the action of light, however, leads to formation of an orange solution in which no new carbonylmetal complex could be detected by IR spectroscopy. Pentacarbonylrhenium bromide precipitates almost completely upon concentrating the solution. After evaporation of the solvent the yellow decomposition product $C_8H_{12}S_3$ **3** could be sublimed out, and this proved to be identical with the product obtained by *Schaumann* and *Grabley*[2] by direct decomposition of **1**.





Of the possible isomers of **3**, *Schaumann* and *Grabley* preferred, on the basis of the two $^{13}C\{^1H\}$-NMR signals [$\delta = 24.22$ (CH_3), 129.19 (C=C)] the 1,2,5-trithiepin structure **3A**. Because of the ^{1}H-NMR signals [$\delta = 1.93$ (s), 2.02 (s)], which are typical of exocyclic isopropylidene groups, and the very intense dimethylthioketene fragment in the mass spectrum (*m/z* 86), the formulation 1,2,4-trithiolane **3B** appeared to us more probable. Trithiolanes are highly stable and are formed in numerous other reactions[3].



Formation of the trithiolane **3B** can be explained by [3+2]cycloaddition of the betaine **1** to the thioketene **4** formed by Wittig reaction. In contrast to the betaine complexes **2**, the elimination of PPh_3 from **1** is thermally activated.

An X-ray structural analysis[4] confirmed the proposed structure **3B** (Fig. 1). The molecule lies on a twofold crystallographic axis (through S1 and the middle of the S2 and S2′ bond); the ring therefore adopts an exact half-chair conformation. In the very similarly constructed bis(cyclo-

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[+] X-ray structure analysis.

[**] Coordination Chemistry of Functionalized Phosphorus Ylides, Part 2. This work was supported by the Deutsche Forschungsgemeinschaft. Part 1: [1].

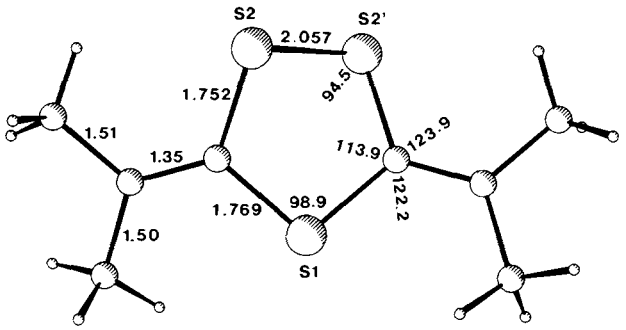

Fig. 1. Molecular structure of **3b** in the crystal. Standard deviations: 0.003, 0.005, and 0.1 Å, respectively, for the S—S, C—S, and C—C bond lengths and 0.2—0.4° for the bond angles.

hexylidene)trithiolane the same C_2 symmetry preference was observed for the whole molecule[3], but was not constrained in this case by crystal symmetry. Presumably in both cases the repulsion of the lone pairs of electrons on the neighboring sulfur atoms leads to this conformation[5].

Procedure

A suspension of $BrRe(CO)_5$ (1.1 g, 2.6 mmol) and **1** (1.0 g, 2.6 mmol) in 40 mL of THF is stirred under reflux for 1 h. After filtration and evaporation of the solvent, **3B** is sublimed out of the residue and recrystallized from ethyl acetate/methanol; yield 160 mg (60%), m.p. = 112—113 °C. The residue from the sublimation contains PPh_3 and Ph_3PS.

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The 1,3-Dithian-2-ylmethoxycarbonyl (Dmoc) Moiety—A Protecting Group for the Amino Function in Peptide Synthesis

By *Regina Barthels* and *Horst Kunz**

Dedicated to Professor Helmut Zahn on the occasion of his 65th birthday

In the synthesis of peptides, and particularly in glycopeptides[8], a sensitive protecting group is required which can be selectively removed under mild conditions. The use of a two-stage protecting group avoids the presence of such sensitive groups during the synthesis: The stable form of the protecting group is converted into a labile form by chemical modification just prior to cleavage.

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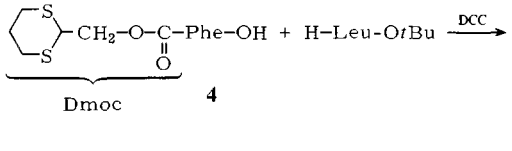
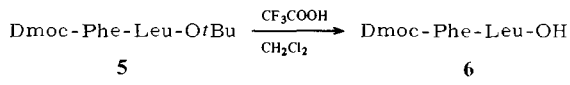
The 2-methylthioethoxycarbonyl (Mtc) group[9] developed by us for the protection of the amino functions in this way in peptide synthesis is quite stable towards bases but not sufficiently so towards strong acids. We therefore converted it into the dithian-2-ylmethoxycarbonyl (Dmoc) group.

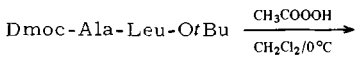


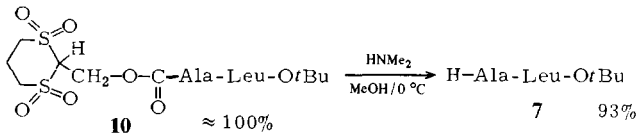


This group can be introduced into amino acid-trimethylbenzylammonium salts *via* the corresponding *p*-nitrophenyl carbonate. With Dmoc amino acids such as **4**, peptide syntheses can be carried out both by the carbodiimide[5] as well as by the mixed anhydride method[6].

Dmoc protection is stable towards trifluoroacetic acid/dichloromethane at 25 °C, so that the *tert*-butyl ester group, *e.g.* in **5**, can be selectively cleaved.

For cleavage, the Dmoc group of the Dmoc-dipeptide ester **9**, which is stable towards acids and bases, is oxidized with peracetic acid to the highly sensitive disulfone **10**.





The protecting group can be completely removed from the oxidized compound **10** with 20% dimethylamine in methanol at 0 °C or with saturated sodium hydrogen carbonate solution according to an E1cB mechanism.

The Dmoc group is thus a reliable amino-protecting group which is stable under the acidic and basic conditions of peptide synthesis, and can be readily removed after simple modification.

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Synthesis of 2-Vinylphosphiranes

By *Wolf Jürgen Richter**

Until now phosphiranes could not be prepared by addition of a phosphanediyl to olefins; both thermolysis of $(PhP)_5$[1] and treatment of organodichlorophosphanes with

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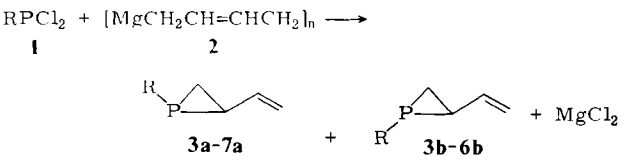
magnesium in presence of olefins led to other compounds[2]. Only the reaction of dichloro(phenyl)phosphane with the dipotassium salt of cyclooctatetraene afforded a phosphirane as primary product[3]. Substituted phosphiranes are accessible by reaction of vicinal dihalides with alkali metal phosphides [*e.g.* NaPHR][4]. We describe here a straightforward route to vinyl-substituted phosphiranes by reaction of organodichlorophosphanes **1** with magnesium butadiene **2**[5].



In addition to cyclooligophosphanes, isomeric 1-alkyl- or 1-phenyl-2-vinylphosphiranes **3**—**7** can be isolated.

At low temperatures a *cis*-1,2-disubstituted phosphirane, which epimerizes at higher temperatures to a *cis*/*trans*-mixture, is predominantly formed. The ^{31}P-NMR signals appear in the region characteristic of substituted phosphiranes ($\delta = -160$ to -220, Table 1); the resonances at lower field stem from the *cis*-isomer, and this was confirmed from the ^{13}C,^{31}P-coupling constants.

Table 1. Selected physical data of vinylphosphoranes **3**—**7**.

Cpd.	R	Yield [%]	B.p. [°C/torr]	^{31}P-NMR (δ-values, C_6D_6) a	b
3	*tert*-Butyl	32	60/20	−160.1	−171.0
4	Cyclohexyl	38	55/0.01	−190.2	−190.3
5	Menthyl	36	68/0.01	−190.1	−191.0
				−190.4 [a]	−197.5 [b]
6	Methyl	10	[c]	−216.1	−216.7
7	Phenyl	2	ca. 60/0.1	−204.5	—

[a] Isomer **5c**. [b] Isomer **5d**; structure not yet confirmed. [c] Not determined.

Use of the (−)-menthyl derivative **1** afforded four diastereoisomers, of which the major component (80%, **5a**) is a *cis*-isomer (^{31}P-NMR: $\delta = -190.1$); the other *cis*-phosphirane (**5c**, $\delta = -190.4$) is formed in *ca.* 8% yield. Consequently, the asymmetric induction amounts to *ca.* 82% de.

The vinylphosphoranes isomerize above 150 °C to yield phospholenes; this reaction also occurs photochemically and under Ni^0 catalysis.

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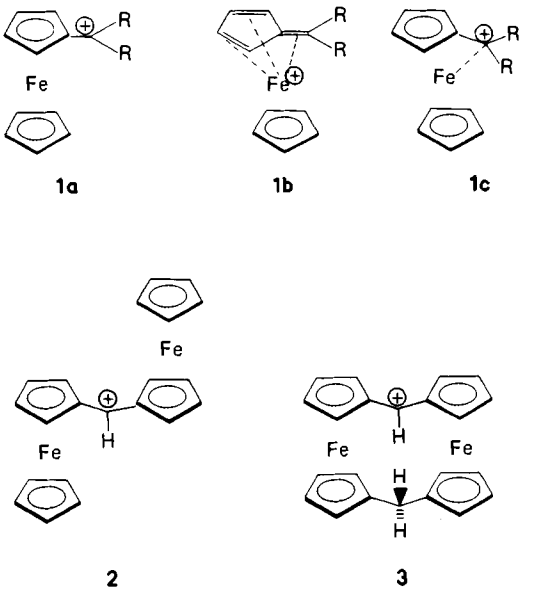
Influence of Conformational Rigidity on the Stabilization of α-Ferrocenyl Carbocations: A *cis*-Fixed Diferrocenyl Carbenium Ion

By *Ulrich T. Mueller-Westerhoff**, *Adel Nazzal*, *Wolfram Prössdorf*, *James J. Mayerle*, and *Russell L. Collins*

To explain the unusual stability of α-ferrocenyl carbenium ions **1**, contributions by structures of different geometries such as **1b** and **1c** have often been proposed. A precise structure determination for the ferrocenyl(diphenyl)carbenium ion **1**. $R = C_6H_5$, indicates[7] that this can best be described by **1c**. On the other hand, *Cais et al.*[8] found that the tetrafluoroborate of the ferrocenyl carbenium ion crystallizes in a *trans*-conformation **2**; both undistorted ferrocenes are, however, bent towards the positively charged central C atom. The structural results leave open the question of how much the bending reflects the stabilization of the isolated molecule as opposed to crystal packing effects.



In the *cis*-fixed diferrocenyl carbenium ion **3** the bridging CH_2 group effectively eliminates twisting and rotation. Any major bending of the carbenium ion center towards one or both of the Fe atoms would be an energetically very unfavorable process. With these constraints is **3** destabilized relative to **2**?

The tetrafluoroborate salt of **3** can be prepared from [1.1]ferrocenophane[15] as shiny black needles, which dissolve in CH_2Cl_2 to give a deep blue-green colored solution. In the UV spectrum the longest wavelength band is in methylene chloride shifted 140 nm bathochromically relative to the corresponding band in **2**. While in [1.1]ferroceno-

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phane rapid exchange between two equivalent *syn*-conformations occurs, the carbenium ion **3** has a rigidly fixed *syn*-conformation: in the ^{1}H-NMR spectrum (CD_2Cl_2) a singlet for the CH proton occurs at $\delta = 7.71$, the bridging CH_2 group appears as two sharp doublets ($\delta = 2.05$ and 2.49, $J = 22$ Hz) and all eight different ferrocene protons can be distinguished.

From the twelve signals in the ^{13}C-NMR spectrum only those of the carbenium C atom ($\delta = 162.3$) and the adjacent C atoms ($\delta = 108.1$) show a significant downfield shift (remaining signals: $\delta = 70-90$).

This conformational rigidity of cation **3** must be attributed to conjugation between the positively charged C atom and both ferrocene units. Nevertheless, the Mössbauer spectra of these two carbenium ions show that **3** has no more positive charge residing on the Fe atoms than its non-bridged counterpart **2**; each ferrocene has accepted one-third of the charge. This reduction in charge on the CH group also can explain the absence of hydride transfer in **3**, whose structure would appear to predestine it to such an exchange. In the corresponding carbanion, rapid proton transfer is known to occur[18].

The X-ray structure of the tetrafluoroborate of **3** shows that: 1) the cation is in a fixed *syn*-conformation; 2) all cyclopentadienyl rings are planar within 1 pm; 3) in the two ferrocene units, the rings are not coplanar but tilted by 6.6 and 7.5°, respectively, opening towards the center of the cation; 4) the Fe—C distances average 206 ± 2 pm and indicate that the Fe atoms are located essentially symmetrically with respect to their ligands; 5) the positively charged C atom is noticeably displaced towards the center of the molecule, lying *ca.* 20 pm below the intersection of the two adjacent cyclopentadienyl rings, with Fe-C$^{\oplus}$ distances of 296 and 301 ± 2 pm. In this way, any overlap between the $2p_z$ orbital of the carbenium C atom and the d orbitals at the iron atoms tends to be maximized, but the rigidity of the cation allows this to happen only to a very limited degree. In contrast to the earlier crystallographic work, we may be confident that, because of the cyclic structure, crystal packing forces cannot contribute significantly to the structural deformation in **3**. The displacement of the carbenium C atom towards the Fe atoms must therefore be associated with the stabilization effect alone.

The three main factors in α-ferrocenyl carbenium ions are therefore: charge distribution from the carbenium C atom to ferrocene, conjugative interaction between the carbenium C atom and the adjacent π-system, and direct Fe—C$^{\oplus}$ bonding. The first two stabilizing factors do not require geometrical changes as in **1b** and **1c**; since the third type of stabilization is significant in **3** (with deformation), we assume that carbenium ions of type **1** can, on the whole, be described by **1c**.

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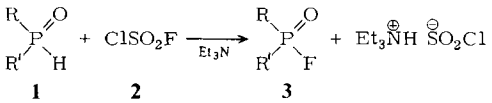
Novel Application of Sulfonyl Chloride Fluoride in the Synthesis of Organophosphorus Fluorine Compounds: Direct Conversion of >P(O)H and >P(O)OH Groups into >P(O)F Groups

By *Andrzej Łopusiński* and *Jan Michalski**

The readily available[1] sulfonyl chloride fluoride **2** has found extensive use as solvent in the spectroscopic investigation of carbocations[2] and is occasionally used in organic synthesis[3]. Recently the organophosphorus fluorine compounds RR'P(O)F and R_3PF_2 have been prepared from sulfides and selenides >P=X[4].

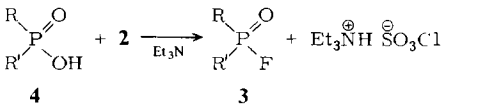
Compounds containing the >P(O)H and >P(O)OH part structures such as **1** and **4**, respectively, show the ability to act as proton donors. We now describe a novel method for their conversion into acid fluorides >P(O)F **3** by the action of **2** under extremely mild conditions.

Dialkyl phosphites and compounds of type **1** react at −40 °C in dichloromethane with **2** in the presence of tertiary amine to give the corresponding fluorides **3**. The most important discovery was that in dichloromethane **2** reacts smoothly at −60 °C with tetracoordinate phosphorus acid salts **4** to give fluorides **3** in very high yield. At higher temperatures the chlorides RR'P(O)Cl are formed in addition to **3**. Presumably the reaction proceeds *via* the mixed anhydrides $RR'P(O)OSO_2Cl$ as reactive intermediates.



1 **2** **3**

a, R = R' = OEt



4 **3**

b, R = *t*Bu, R' = Ph

Experimental

3b: **2** (1.5 g, 0.012 mol) was added to a solution of *tert*-butyl(phenyl)phosphinic acid **4b** (1.9 g, 0.01 mol) in 15 mL of CH_2Cl_2 and Et_3N (1.0 g, 0.01 mol) at −65 °C. The reaction mixture was stirred at −55 °C to −60 °C for 2 h and held at 0 °C for additional 6 h. The solution was washed with 15 mL of H_2O and the organic layer dried over $MgSO_4$. Distillation gave 1.5 g (75%) of *tert*-butyl(phenyl)phosphinic acid fluoride **3b**, b.p. = 68−70 °C/0.2 torr, $\delta(^{31}P) = +58.63$, $J_{PF} = 1048$ Hz, $\delta(^{19}F) = +98.34$ ($CFCl_3$ int.).

3a: Diethylfluorphosphate **3a** was obtained in a similar procedure from **1a** (1.3 g, 0.01 mol), Et_3N (1.0 g, 0.01 mol), and **2** (1.5 g, 0.012 mol) at −40 °C in 85% yield: b.p. = 59−60 °C/12 torr, $\delta(^{31}P) = -9.4$, $J_{PF} = 964$ Hz.

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Relaxation Studies on the Stabilization of Trityl Cations by Acids**

By *Franz L. Dickert** and *Helmut Fackler*

Superacids enable the preparation of extremely reactive carbenium ions[1]. The well stabilized trityl cations $Trt^{\oplus}$, on the other hand, are already obtained from triphenylmethanol by acids of the strength of usual mineral acids[2]. Thus, in the case of ionogenic trityl trifluoroacetate Trt(TFA) the conductivity in acetonitrile increases considerably on addition of trifluoroacetic acid H(TFA)[3a]. This is not due to the conductivity of the acid, which is practically undissociated in acetonitrile[3b], but to formation of trityl cations:

$$Trt(TFA) \underset{k_{12}}{\overset{k_{21}}{\rightleftharpoons}} Trt^{\oplus} + TFA^{\ominus} \qquad (1)$$

To explain this increase in conductivity we carried out a series of relaxation studies[4] (pressure-jump method with conductivity detection and optical observation). The findings in Figure 1[3c] indicate that ion-pair formation can be

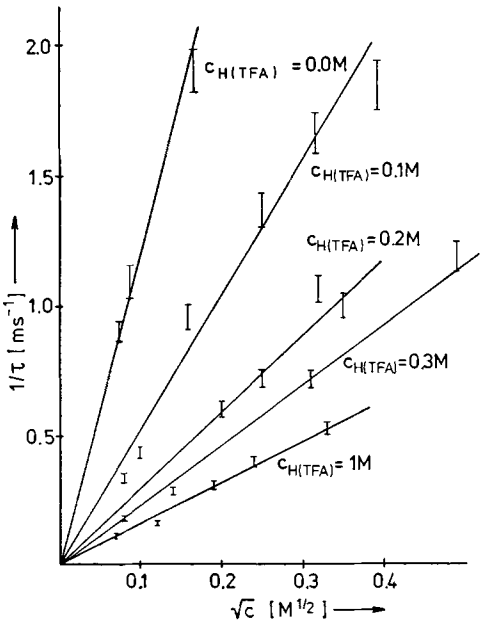

Fig. 1. Reciprocal relaxation times $1/\tau$ as a function of the total concentrations of trityl trifluoroacetate in acetonitrile (273 K) at variable concentrations of added trifluoroacetic acid.

neglected as preliminary step during ion recombination according to eq. (1).

Table 1. Rate constants of ion recombination k_{12}, activation parameters, and rate constants of dissociation k_{21} for trityl trifluoroacetate in trifluoroacetic acid-acetonitrile.

$c_{H(TFA)}$ [mol/L]	k_{12}(273 K) [L mol^{-1} s^{-1}]	ΔH_{12}^{+} [kJ·mol^{-1}]	ΔS_{12}^{+} [J·K^{-1} mol^{-1}]	k_{21}(273 K) [s^{-1}]
0.0	$(6.0\pm2.0)\times10^{6}$	28±3	−24±4	6.9±0.4
0.1	$(8.2\pm0.8)\times10^{5}$	29±3	−22±4	11.0±0.6
0.2	$(2.1\pm0.2)\times10^{5}$	31±3	−17±4	11.0±0.9
0.3	$(1.7\pm0.2)\times10^{5}$	36±3	− 9±4	11.0±1.2
1.0	$(6.8\pm0.7)\times10^{4}$	44±3	+ 9±4	11.0±1.8

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The rate constants and activation parameters are listed in Table 1. k_{21} was determined by ^{19}F-NMR measurements independently of the relaxation investigations[3b]. The shift of the dissociation equilibrium (1) in favor of the formation of trityl cations on addition of acid is due to a drastic reduction in k_{12}. Trifluoroacetic acid, having an acceptor number AN = 105.3 on the Gutmann scale[5], solvates anions extremely effectively *via* hydrogen bonding; hence, the nucleophilicity of the trifluoroacetate ions is reduced more and more with increasing acid concentration. Addition of acid has little effect on k_{21}. As already observed in previous experiments[3b], trityl trifluoroacetate and trifluoroacetic acid form a 1:1 complex. This leads to a slight increase in k_{21} (Table 1).

Accordingly, eq. (1) must be modified by two additional solvation equilibria:

$$\begin{array}{l} Trt(TFA) + n\ H(TFA) \\ \quad\uparrow\downarrow \\ Trt(TFA)\ldots H(TFA) + (n-1)\ H(TFA) \\ \quad\downarrow\uparrow \\ Trt^{\oplus} + (TFA)^{\ominus}\ldots[H(TFA)]_n \end{array} \qquad (2)$$

Hence, rapid desolvation of the anions precedes ion recombination. In agreement with this hypothesis is the finding that ΔH_{12}^{+} increases on addition of acid (Table 1). The experimentally determined activation enthalpy ΔH_{12}^{+} is then made up of the positive anion-desolvation enthalpy ΔH_{12}^{0} and the activation enthalpy $\Delta H_{12}^{+}(0)$ in absence of acid:

$$\Delta H_{12}^{+} = \Delta H_{12}^{0} + \Delta H_{12}^{+}(0) \qquad (3)$$

From eq. (1) and the results in Table 1, a value of 16 kJ/mol is obtained for ΔH_{12}^{0} in 1 M trifluoroacetic acid solution. This enthalpic effect outweighs the increase in activation entropy in the temperature range investigated and leads to strongly reduced ion-recombination rate constants k_{12}.—In this way the formation of carbenium ions is favored when solutions of ionogens are treated with acid.

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High-Field Conditioned NMR Spin Decoupling in Organomercury Compounds

By *Reinhard Benn, Harald Günther**, *Adalbert Maercker, Volkmar Menger*, and *Peter Schmitt*

Of the mechanisms which influence spin-lattice relaxation rates R_1 ($=1/T_1$) in nuclear magnetic resonance, the contribution from the chemical shift anisotropy

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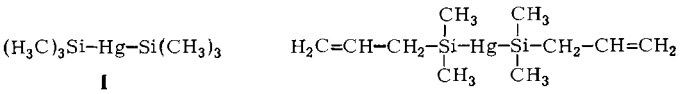
(R_1^{CSA}) not only depends on the correlation time τ_c but also on the magnetic flux density B_0[1]:

$$R_1^{CSA} = (2/15)\gamma_I^2 B_0^2 [\Delta\sigma^2]\tau_c$$

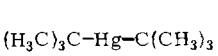
If R_1^{CSA} is the most important parameter for a given magnetic nucleus, the high magnetic fields available today from cryomagnets, may lead to very rapid relaxation. In the case of spin-spin coupling this can cause line broadening for neighboring nuclei or even spin, spin-decoupling.

Heavy metal nuclei such as ^{199}Hg in linear molecules of the type R—Hg—R exhibit relatively high chemical shift anisotropies, whose significance for the observed relaxation behavior has recently been stressed[2]. We show here that with silylmercury compounds, high-field NMR spectroscopy can lead to the disappearance of ^{199}Hg, ^{1}H-spin,spin coupling and, in consequence, to a loss of information.



1

2



3

The ^{1}H- and ^{13}C-NMR spectra of bis(trimethylsilyl)mercury **1**, respectively, at 1.88 T ($\nu_0(^1H) = 80$ MHz), show the expected satellite lines (Fig. 1) due to $^3J(^{199}Hg,^1H)$ and $^2J(^{199}Hg,^{13}C)$ spin-spin coupling. When the same sample is measured at 9.4 T ($\nu_0(^1H) = 400$ MHz) selective line broadening occurs, which in the ^{1}H-NMR spectrum practically leads to loss of the coupling. The same effect was observed with bis(allyldimethylsilyl)mercury **2**, and even with di-*tert*-butylmercury **3**.

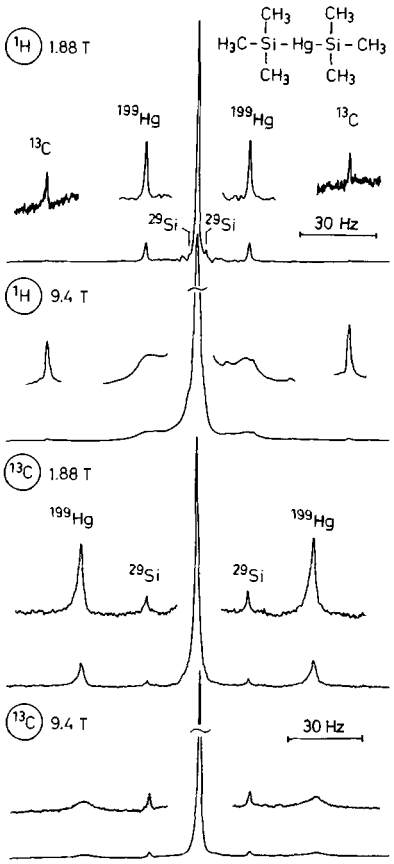


Fig. 1. ^{1}H- and ^{13}C-NMR spectra of bis(trimethylsilyl)mercury **1** [5] at 1.88 and 9.4 T; the ^{13}C-NMR spectrum is broadband decoupled. The following coupling constants are obtained from the satellite spectra: $^1J(^{13}C,^1H) = 119.6$; $^2J(^{29}Si;^1H) = 6.6$, $^3J(^{199}Hg,^1H) = 40.7$; $^1J(^{13}C,^{29}Si) = 40.1$, $^2J(^{13}C,^{199}Hg) = 92.1$ Hz.

That enhanced spin-lattice relaxation of the ^{199}Hg nucleus is indeed involved is shown by the fact that the satellite lines produced by $^1J(^{13}C,^1H)$- and $^1J(^{13}C,^{29}Si)$ coupling remain sharp (Fig. 1)[3a]; it also becomes apparent from the T_1 data. As shown in Table 1 the T_1 values measured at three different field strengths closely follow the ratio $(B_0^{(i)}/B_0^{(j)})^2$, so that even at 1.88 T, R_1^{CSA} must provide the predominant contribution to the relaxation of the ^{199}Hg nucleus[3b].

Table 1. ^{199}Hg spin-lattice relaxation times T_1 [ms] for **1**, **2**, and **3** at various magnetic flux densities B_0[T] [a].

B_0	1.88	6.35	9.40
1	460	45.4	21.5
2	310	29.1	18.6
3	1280	136	63.5

[a] Measured using the inversion recovery method [1] with Bruker WP 80, WH 270, and WH 400 spectrometers; $\nu_0(^{199}Hg) = 14.3$, 48.2 and 71.7 MHz, respectively; solvent C_6D_6/C_6H_6 (9:1); conc.: 30 wt.-%

Since R_1^{CSA} is also of significance with other metal nuclei[4], the possibility of enhanced spin-lattice relaxation must be considered in high-field NMR studies of organometallic compounds in order to prevent erroneous assignments, particularly since broad residual signals can disappear in the noise.

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[3] a) In small molecules ^{13}C and ^{29}Si usually relax by the field-independent dipolar mechanism. b) Apparently because of the nonlinear structure of **2**, the field-strength dependence is observed to a lesser extent.
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$(\mu\text{-H})_3[C_5H_5RhP(iPr)_3]_2^+$: A Dinuclear (Rh—Rh) Complex with Three Bridging Hydrido Ligands

By *Helmut Werner** and *Justin Wolf*

Hydrido(phosphane)rhodium compounds play an important role as catalysts or as intermediates in catalytic hydrogenations (*e.g.* with $Rh(PPh_3)_3Cl$)[1]. Recently, we have been particularly interested in the behavior of the Lewis basic alkyne(phosphane)complexes $C_5H_5Rh(C_2R_2)P(iPr)_3$ with Brønsted acids[2], and in this connection have attempted preparation of the dihydrido(phosphane)complex **3** from $RhClH_2[P(iPr)_3]_2$[3] and NaC_5H_5. However, only small amounts of **3** are formed in this reaction.

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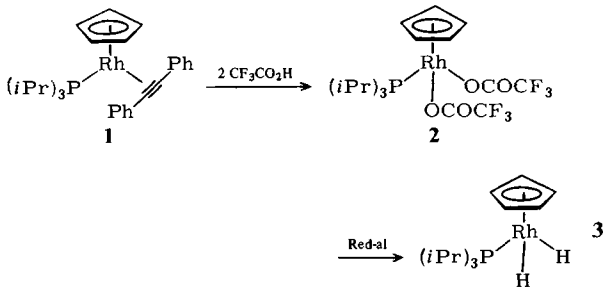
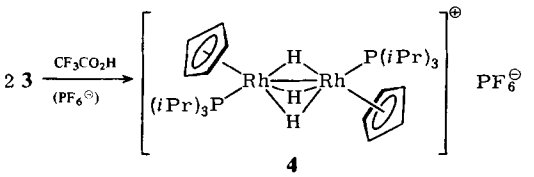
Another method has proved to be considerably more propitious: Compound **1**, which reacts with an equimolar amount of trifluoroacetic in diethyl ether to give $C_5H_5Rh(CPh{=}CHPh)(OCOCF_3)P(iPr)_3$[2], reacts with excess CF_3CO_2H at 40 °C to afford the bis(trifluoroacetato)complex **2** [^{1}H-NMR ($CDCl_3$): $\delta = 6.09$ (dd, $J_{PH} = 1.7$, $J_{RhH} = 0.6$ Hz (C_5H_5)); IR (KBr): $\nu(CO) = 1680$ cm^{-1}]. Treatment of **2** with $Na[AlH_2(OC_2H_4OMe)_2]$ ("Red-al") in toluene/ether at 20 °C gives the colorless, highly air-sensitive dihydridorhodium compound **3** in 36% yield which melts below room temperature [^{1}H-NMR (C_6H_6): $\delta =$ 5.55 (m(C_5H_5)); −14.73 (dd, $J_{PH} = 33.5$, $J_{RhH} = 27.5$ Hz (RhH_2)); IR (hexane): $\nu(RhH) = 2045$ cm^{-1}]. In a similar manner *Maitlis et al.*[4a] and *Bergman et al.*[4b] recently synthesized the complexes $C_5Me_5RhH_2PR_3$ (R = Me, Ph) starting from $C_5Me_5Rh(OCOCH_3)_2PMe_3$ and $C_5Me_5RhCl_2(PPh_3)$, respectively, and starting from $C_6Me_6Ru(OCOCF_3)_2PR_3$ we synthesized the complexes $C_6Me_6RuH_2PR_3$ ($R_3 = Me_3$, $MePh_2$, Ph_3)[4c].



Whereas **3** is inert towards alkenes (*e.g.* C_2H_4) or alkynes (*e.g.* C_2H_2, C_2Ph_2) under standard conditions, a rapid reaction takes place with CF_3CO_2H in methanol in presence of NH_4PF_6. The violet crystalline solid **4**, which is air-stable for a short time but which decomposes fairly rapidly in solution, is formed accompanied by evolution of H_2. Elemental analysis, conductivity (in MeOH: $\Lambda = 103$ cm$^2\,\Omega^{-1}$ mol^{-1}), and NMR data confirm the composition. In addition to the ^{1}H-NMR spectrum [(CD_3NO_2): $\delta = 5.64$ (d, $J_{PH} = 1.1$ Hz (C_5H_5)), −17.75 (tt, $J_{PH} = 13.1$, $J_{RhH} = 13.1$ Hz (RhH_3Rh))] the ^{31}P-NMR (in CD_3NO_2) supports the structural proposal: a 6 line signal corresponding to an XAA'X' spin system (AA' = Rh; X, X' = P) is observed for the phosphane P atoms at $\delta = 80.22$; the coupling constants are $^1J_{RhP} = 141.1$, $^3J_{RhP} = 1.8$, $J_{RhRh} = 11.4$ Hz.



To the best of our knowledge **4** is the first dinuclear (Rh—Rh) complex with three bridging hydrido ligands. By considering an M—M bond, each rhodium atom (which is in oxidation state III) achieves the 18 electron configuration. The cation $[(C_5Me_5Ir)_2(\mu\text{-}H)_3]^+$, with a very short Ir—Ir distance, is known for iridium(III); the dinuclear rhodium cations $[(C_5Me_5Rh)_2(\mu\text{-}H)_2(\mu\text{-}OCOR)]^+$ and $[(C_5Me_5Rh)_2(\mu\text{-}H)(\mu\text{-}OCOR)_2]^+$ ($R = CH_3$, CF_3) are similar in this respect[5]. The reactivity and structural data of these two complexes suggest[5] that the hydrido bridges stabilize the dinuclear structure, and this undoubtedly also applies to **4**.

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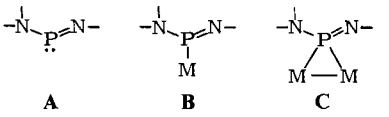
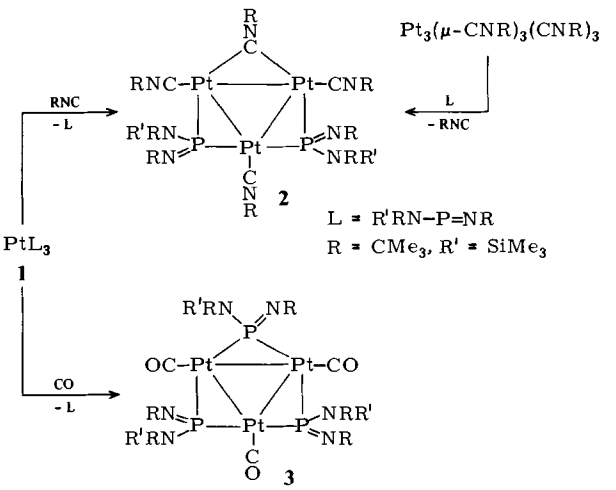
λ^3-Phosphazenes as Bridging η^1-Ligands**

By *Otto J. Scherer*, Rainer Konrad, Ernst Guggolz*, and *Manfred L. Ziegler*

By analogy to metal complexes with *e.g.* CO- or RNC-ligands, λ^3-phosphazenes **A** [amino(imino)phosphanes] should be capable also of participating in terminal (**B**) as well as in bridging (**C**) coordination schemes.



Until now, phosphazene complexes characterized by structure-analytical methods with ligands of type **A** exhibit, without exception, the end-on ligand arrangement **B**[1,2]. The platinum trinuclear clusters **2** and **3**, in which a σ^2, λ^3-phosphorus compound[3] participates in μ-*P* coordination **C** have been realized for the first time. They can be prepared in good yield from PtL_3 **1**[1] and isocyanides, and carbon monoxide, respectively.



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2, which can also be obtained from $Pt_3(\mu\text{-}CNR)_3(CNR)_3$[4] and λ^3-phosphazene L, forms orange crystals which are highly soluble in benzene, ether, and dichloromethane, and moderately soluble in pentane. **3** is sparingly soluble in benzene, and moderately soluble in CCl_4 and CH_2Cl_2 (whereby **3** decomposes faster than **2**). In the IR spectrum of **2** (in CH_2Cl_2) the RNC bands occur at 2150 vs, 2080 w (terminal), and 1775 s, 1730 sh cm^{-1}

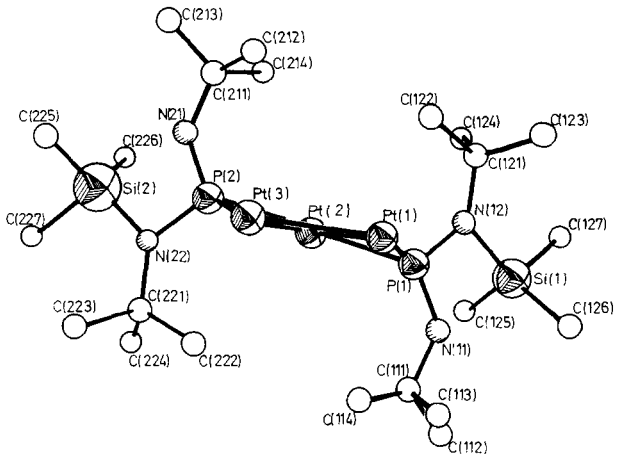

Fig. 1. ORTEP representation of complex **2** (side view without RNC ligands; thermal vibration ellipsoids with 50% probability). Most important bond lengths [pm] and angles [°] of the μ_2,η^1-phosphazene ligands: P(1)—Pt(1) 231.9(6), P(1)—Pt(2) 233.8(7), P(2)—Pt(2) 236.8(8), P(2)—Pt(3) 231.9(7), P(1)—N(11) 157.7(3), P(1)—N(12) 166.0(2), P(2)—N(21) 151.2(3), P(2)—N(22) 169.6(3); N(11)—P(1)—N(12) 97.3(1), N(21)—P(2)—N(22) 95.8(2); sum of angles at N(12) 359.9, N(22) 358.8.

(both br., bridging). In **3** (KBr disc) νCO appears in the region expected for terminal ligands (2045 vs, 2000 w, 1980 sh cm^{-1}). The structures of **2** and **3** were confirmed by crystal structure analysis (Fig. 1).

In **2** and **3** the distances and angles in the comparable parts of the cluster framework deviate only slightly from those in $Pt_3(\mu\text{-}CNR)_3(CNR)_3$[4]. Figure 1 illustrates the *trans*-orientation of both imino groups and the *trans*-configuration of the residue on the P=N bond necessary for migration of the $(CH_3)_3Si$ group (readily detectable by NMR spectroscopy). Compared to free L (104.9°)[12] and PtL_3 (average value *ca.* 104°)[2] an unusually small NPN angle (average value 96.5°) is exhibited by L in **2**. This angle opens slightly in **3** (average value 101.5°) whose *P*-imino groups are arranged mutually *trans/cis/trans*.

In comparison to the $^{31}P\{^1H\}$-NMR spectrum of the noncoordinated λ^3-phosphazene L ($\delta = 327.5$) that of **2** ($\delta = 286.7$) shows a weak, and that of **3** ($\delta = 237.3$), a strong high-field shift.

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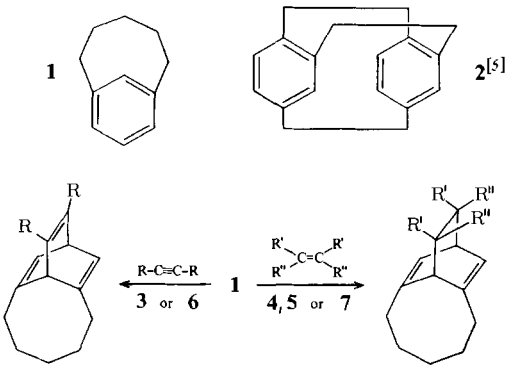
Diels-Alder Reactions of [5]Metacyclophane

By *Lucas A. M. Turkenburg, Pieter M. L. Blok, Willem H. de Wolf,* and *Friedrich Bickelhaupt**

[5]Metacyclophane **1**, the smallest compound of its class known so far[8], is highly strained and thus can be expected to show a markedly reduced aromaticity. To check this, we investigated its reactivity in Diels-Alder reactions. Dienophilic alkynes such as **3** and **6** (Table 1) add to **1** as anticipated with formation of the 2,6-pentamethylenebarrelenes **8a** and **8b**, respectively, while reaction of **4**, **5**, or **7** and **1** affords the 2,6-pentamethylene-7,8-dihydrobarrelenes **9**; in no case were byproducts observed.



8a, R = CF_3
8b, R = $COOCH_3$

9a, R' = R'' = CN
9b, R' = H, R'' + R'' = CO—O—CO
9c, R' = H, R'' = $COOCH_3$

Table 1. Diels-Alder reactions of **1** and **2** [5].

Dienophile	**1**	**2**
4-Phenyl-1,2,4-triazoline-3,5-dione		C_6H_6, 20 °C, 3 h, 79%
Hexafluoro-2-butyne **3**	$CDCl_3$, 20 °C, < 1 h, 100%	
Tetracyanoethene **4**	$CDCl_3$, 20 °C, 15 min, 100%	C_6H_6, 20 °C, 20 h, 59%
Maleic anhydride **5**	$CDCl_3$, 20 °C, 15 min, 100%	C_6H_6, 100 °C, 10 h, 53%
Acetylenedicarboxylic acid dimethyl ester **6**	$CDCl_3$, 20 °C, 5 h, 100%	C_6H_6, 170 °C, 1 h, 61%
Dimethyl maleate **7**	C_6H_{12}, 65 °C, 25 h, 77%	C_6H_6, 100 °C, 10 h, 0%
Cyclopentene	C_6D_{12}, 80 °C, 64 h, 0%	

In Table 1 the results of the Diels-Alder reactions of **1** are compared with those of the reactive, likewise mononuclear benzene derivative [2$_3$](1,2,4)cyclophane **2**[5]. It emerges that **1** is considerably more reactive than **2**. This is strikingly demonstrated by its behavior towards the two weakly dienophilic compounds **6** and **7**. **6** reacts quantitatively with **1**, even at room temperature, whereas for reaction with **2** a temperature of 170 °C is necessary. In the case of **7**, **2** apparently stays below the limit of reactivity, while a satisfactory reaction rate is still observed for **1** at 65 °C. Only with cyclopentene, which is just about three times less reactive than **7** towards 9,10-dimethylanthracene in dioxane[9], could a reaction no longer be established for **1**, even at 80 °C.

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2, which can also be obtained from $Pt_3(\mu\text{-}CNR)_3(CNR)_3$[4] and λ^3-phosphazene L, forms orange crystals which are highly soluble in benzene, ether, and dichloromethane, and moderately soluble in pentane. **3** is sparingly soluble in benzene, and moderately soluble in CCl_4 and CH_2Cl_2 (whereby **3** decomposes faster than **2**). In the IR spectrum of **2** (in CH_2Cl_2) the RNC bands occur at 2150 vs, 2080 w (terminal), and 1775 s, 1730 sh cm^{-1}

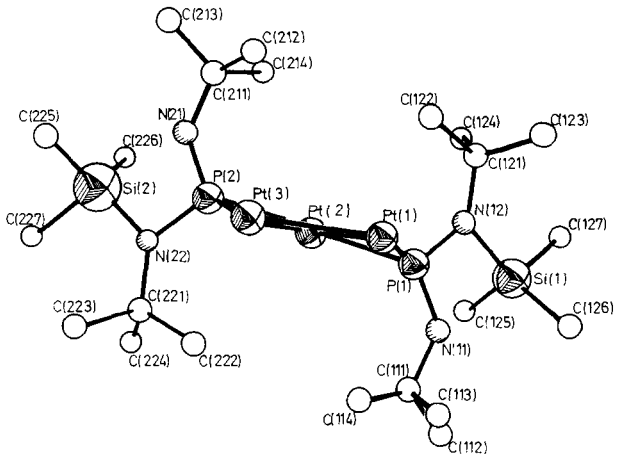

Fig. 1. ORTEP representation of complex **2** (side view without RNC ligands; thermal vibration ellipsoids with 50% probability). Most important bond lengths [pm] and angles [°] of the μ_2,η^1-phosphazene ligands: P(1)—Pt(1) 231.9(6), P(1)—Pt(2) 233.8(7), P(2)—Pt(2) 236.8(8), P(2)—Pt(3) 231.9(7), P(1)—N(11) 157.7(3), P(1)—N(12) 166.0(2), P(2)—N(21) 151.2(3), P(2)—N(22) 169.6(3); N(11)—P(1)—N(12) 97.3(1), N(21)—P(2)—N(22) 95.8(2); sum of angles at N(12) 359.9, N(22) 358.8.

(both br., bridging). In **3** (KBr disc) νCO appears in the region expected for terminal ligands (2045 vs, 2000 w, 1980 sh cm^{-1}). The structures of **2** and **3** were confirmed by crystal structure analysis (Fig. 1).

In **2** and **3** the distances and angles in the comparable parts of the cluster framework deviate only slightly from those in $Pt_3(\mu\text{-}CNR)_3(CNR)_3$[4]. Figure 1 illustrates the *trans*-orientation of both imino groups and the *trans*-configuration of the residue on the P=N bond necessary for migration of the $(CH_3)_3Si$ group (readily detectable by NMR spectroscopy). Compared to free L (104.9°)[12] and PtL_3 (average value *ca.* 104°)[2] an unusually small NPN angle (average value 96.5°) is exhibited by L in **2**. This angle opens slightly in **3** (average value 101.5°) whose *P*-imino groups are arranged mutually *trans/cis/trans*.

In comparison to the $^{31}P\{^1H\}$-NMR spectrum of the noncoordinated λ^3-phosphazene L ($\delta = 327.5$) that of **2** ($\delta = 286.7$) shows a weak, and that of **3** ($\delta = 237.3$), a strong high-field shift.

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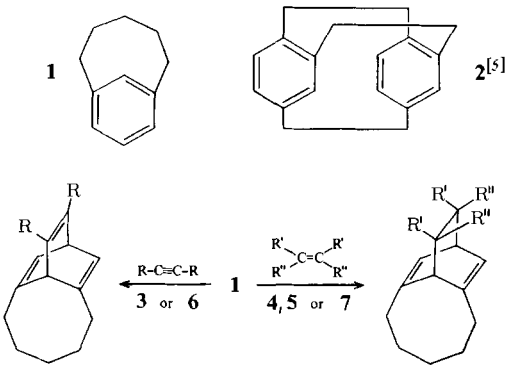
Diels-Alder Reactions of [5]Metacyclophane

By *Lucas A. M. Turkenburg, Pieter M. L. Blok, Willem H. de Wolf,* and *Friedrich Bickelhaupt**

[5]Metacyclophane **1**, the smallest compound of its class known so far[8], is highly strained and thus can be expected to show a markedly reduced aromaticity. To check this, we investigated its reactivity in Diels-Alder reactions. Dienophilic alkynes such as **3** and **6** (Table 1) add to **1** as anticipated with formation of the 2,6-pentamethylenebarrelenes **8a** and **8b**, respectively, while reaction of **4**, **5**, or **7** and **1** affords the 2,6-pentamethylene-7,8-dihydrobarrelenes **9**; in no case were byproducts observed.



8a, R = CF_3
8b, R = $COOCH_3$

9a, R' = R'' = CN
9b, R' = H, R'' + R'' = CO—O—CO
9c, R' = H, R'' = $COOCH_3$

Table 1. Diels-Alder reactions of **1** and **2** [5].

Dienophile	**1**	**2**
4-Phenyl-1,2,4-triazoline-3,5-dione		C_6H_6, 20 °C, 3 h, 79%
Hexafluoro-2-butyne **3**	$CDCl_3$, 20 °C, < 1 h, 100%	
Tetracyanoethene **4**	$CDCl_3$, 20 °C, 15 min, 100%	C_6H_6, 20 °C, 20 h, 59%
Maleic anhydride **5**	$CDCl_3$, 20 °C, 15 min, 100%	C_6H_6, 100 °C, 10 h, 53%
Acetylenedicarboxylic acid dimethyl ester **6**	$CDCl_3$, 20 °C, 5 h, 100%	C_6H_6, 170 °C, 1 h, 61%
Dimethyl maleate **7**	C_6H_{12}, 65 °C, 25 h, 77%	C_6H_6, 100 °C, 10 h, 0%
Cyclopentene	C_6D_{12}, 80 °C, 64 h, 0%	

In Table 1 the results of the Diels-Alder reactions of **1** are compared with those of the reactive, likewise mononuclear benzene derivative [2$_3$](1,2,4)cyclophane **2**[5]. It emerges that **1** is considerably more reactive than **2**. This is strikingly demonstrated by its behavior towards the two weakly dienophilic compounds **6** and **7**. **6** reacts quantitatively with **1**, even at room temperature, whereas for reaction with **2** a temperature of 170 °C is necessary. In the case of **7**, **2** apparently stays below the limit of reactivity, while a satisfactory reaction rate is still observed for **1** at 65 °C. Only with cyclopentene, which is just about three times less reactive than **7** towards 9,10-dimethylanthracene in dioxane[9], could a reaction no longer be established for **1**, even at 80 °C.

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Thus **1** is the most reactive of all mononuclear benzene derivatives in [4+2]-cycloadditions, *i.e.* it has the most pronounced cyclohexatriene character.

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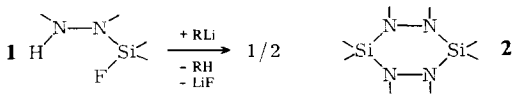
A Stable Diazasilacyclopropane**

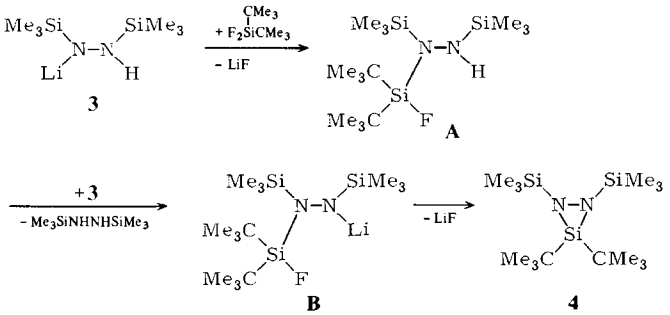
By *Johann Hluchy* and *Uwe Klingebiel**

The first synthesis of a three-membered, silicon-containing ring, azadisilacyclopropane, was reported by *Fink* in 1963[1]. In the meantime the synthesis of other silicon-element three-membered ring systems have been accomplished[2–4]. We now report the synthesis of a diazasilacyclopropane.



Fluorosilyl-substituted hydrazines **1** react with bases such as butyllithium to give preferably six-membered heterocycles **2**[7].

The bulky di-*tert*-butyl(fluoro)silyl group of the hydrazine derivative **A**, which is formed on reaction of singly lithiated *N,N'*-bis(trimethylsilyl)hydrazine **3** with di-*tert*-butyldifluorosilane, reacts with excess **3** with formation of the diazasilylcyclopropane **4**.



The intermediate **A** is not isolated; it reacts with **3**, undergoing transmetalation *via* the lithium salt **B** to give the product **4**. Above +80 °C, and on attempted distillative or gas-chromatographic purification of **4**, di-*tert*-butylbis(trimethylsilylamino)silane $(Me_3SiNH)_2Si(CMe_3)_2$ is formed. The diazasilacyclopropane **4** can be purified by repeated recrystallization from *n*-hexane at −15 °C.

The upfield shift of the ^{29}Si-NMR signal of the silicon-containing small ring compounds is also observable in the case of **4** (in C_6F_6, TMS int.: $\delta = -30.73$)[2,4].

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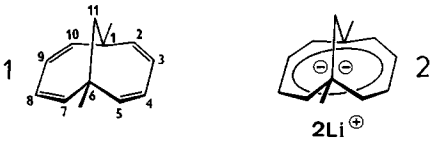
A Bishomocyclooctatetraene Dianion**

By *Walter Huber, Klaus Müllen**, *Ralf Busch, Wolfram Grimme*, and *Jürgen Heinze*

According to recent studies it would appear that homo- and bishomoconjugation[1] are of little or no significance in neutral and anionic π systems[2,3]. In the 1,6-dimethylbicyclo[4.4.1]undeca-2,4,7,9-tetraene **1**[4], a vinylogue of norbornadiene, "through-space" interaction of the p_π orbitals at centers 2 and 10, and at 5 and 7 enables formation of a monocyclic conjugated π-system. We describe here the long sought bishomocyclooctatetraene dianion **2**, which has been generated by reduction of **1**.



A degassed solution of **1** in [D$_8$]tetrahydrofuran ([D$_8$]THF) reacts at −78 °C with lithium to give a deep-red solution of the diamagnetic dilithium compound **2**. Methylation leads to formation of an isomeric mixture of dimethyl derivatives ($C_{15}H_{22}$), and confirms the existence of a doubly negative hydrocarbon system; the ^{1}H- and ^{13}C-NMR spectra of **2** are characteristic of a symmetry which leaves no doubt that the original molecular ring system has remained intact.

The NMR signals of the ring protons of **2** are shifted upfield compared to those of **1**, though to a lesser extent than would be expected as a result of charge effects (see Table 1). This finding and the upfield shift for 11-H (about 3.3 ppm) are consistent with a diatropic 10π-system.

Further evidence for the expected π-bond delocalization is provided by exact analysis of the AA'BB' spin system of the ring protons and correlation of the coupling constants of the vicinal protons with π-bond orders. Accordingly **1** is a diene system with fixed double bonds, while **2** exists as a π-bond delocalized species.

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Table 1. ^{1}H- and ^{13}C-NMR chemical shifts and H,H coupling constants (in Hz) of **1** and **2**.

Position		1(6)	2(5,7,10)	3(4,8,9)	CH_3	11
δ_H	**1** [a]	—	5.41	5.45	1.25	2.53
	2 [b]	—	4.49	4.29	0.49	−0.77
δ_C	**1** [c]	44.4	140.8	122.3	31.6	50.8
	2 [d]	41.9	95.2 [e]	88.8 [e]	41.9	49.0
		J_{23}	J_{24}	J_{25}	J_{34}	
	1	11.60	0.58	0.97	7.19	
	2	8.61	1.21	0.16	7.93	

[a] $CDCl_3$, 400 MHz, 35 °C [19]. [b] [D_8]THF, 90 MHz, −20 °C. [c] $CDCl_3$, 20 MHz, 35 °C. [d] [D_8]THF, 22 MHz, −20 °C. [e] Assignment not confirmed.

A comparison of the ^{13}C-NMR spectra of **1** and **2** reveals the upfield shift of the signals of **2** characteristic for a dianion.

If the formation of **2** is accompanied by pronounced conjugative stabilization, then transfer of the second electron (conversion of the radical anion into the dianion) should be facilitated. The transfer of two electrons, and an ECE mechanism, could be demonstrated cyclovoltammetrically (THF, 0.2 M $NaBPh_4$, Ag as quasi-reference electrode). In a reversible E-step ($E_1^0 \cong -2.1$ V) a radical anion is formed which is then converted in a rapid irreversible C-step into a conjugatively stabilized π system. This conversion favors formation of the dianion, and the redox potential of the second electron transfer shifts anodically ($E_2^0 \cong -1.8$ V; *i.e.* $E_2^0 > E_1^0$). Conversely, in the case of reduction of two neighboring butadiene moieties, E_2^0 would be shifted cathodically compared with E_1^0.

There are convincing arguments against a bishomoconjugation in the neutral and anionic π system considered earlier[1-3]. Our findings clearly show that, for steric and electronic reasons—equal "through space" coupled π fragments are present—**2** is a bishomoconjugatively-stabilized species with ten π electrons.

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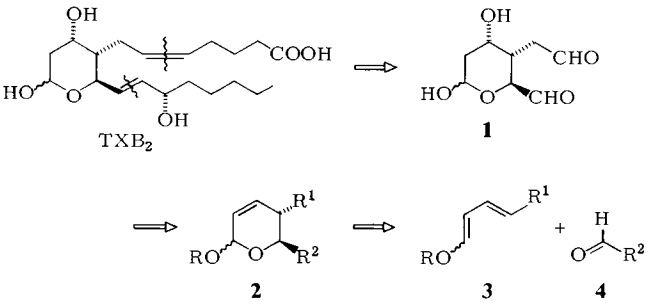
[19] We thank Prof. Dr. H. Günther, Siegen, for recording the 400-MHz ^{1}H-NMR spectrum.

Hetero Diels-Alder Reactions for the Synthesis of Thromboxane Intermediates**

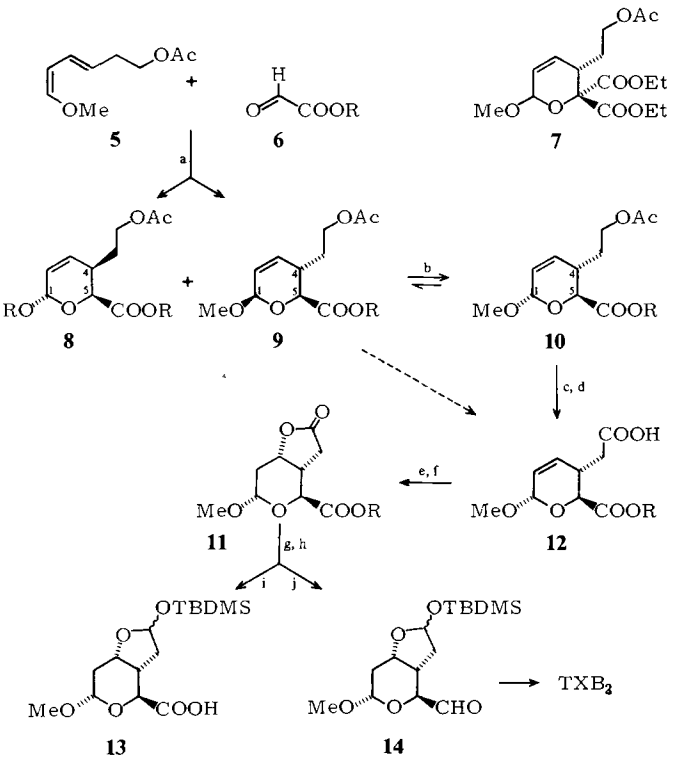
By *Richard R. Schmidt** and *Wolfgang Abele*

Reactive pseudoglycals, which are useful intermediates for the synthesis of modified carbohydrates, have been synthesized by hetero Diels-Alder reactions[1]. This type of reaction should also be useful for the synthesis of the carbohydrate-derived thromboxanes such as TXB_2 (Scheme 1).



Scheme 1.

Exploitation of the hetero Diels-Alder reaction for the synthesis of the target molecule **2**, which has a pseudoglycal structure, requires: (i) a 1-alkoxy-1,3-diene **3** bearing a substituent R^1 which contains two C-atoms and enables stereospecific incorporation of the OH group at C-3 in **2** as well as coupling of the side chain, and (ii) a carbonyl compound **4**, whose substituent R^2 increases the dienophilicity and allows construction of the second side chain.



6, **8**–**12**, R = (−)-Menthyl

Scheme 2. Only the D-isomers are shown. TBDMS = *tert*-butyl(dimethyl)silyl. a: C_6H_6, 120 °C, 72 h; yield 62% (**8**: 31%, **9**: 26%, **10**: 5%) or CH_2Cl_2, 60 °C, 96 h, 8.5 kbar; yield 71% (**8**: 35%, **9**: 30%, **10**: 6%). b: Et_2O, $BF_3 \cdot OEt_2$, RT; yield 100% **10**, colorless oil. c: MeOH, Na_2CO_3, RT, 12 h; yield 75%. d: Dimethylformamide (DMF), pyridinium dichromate, RT, 8.5 h; yield 57% **12**, m.p. 166—168 °C (*n*-hexane). e: Tetrahydrofuran (THF), KI/I_2, RT, 5 h; yield 94%. f: Toluene, *n*-Bu_3SnH, 80 °C, 30 h; yield 92% **11**, colorless oil. g: Toluene, DIBAH, −70 °C, 20 h; yield 70%. h: DMF, TBDMS-Cl, 40 °C, 1.5 h; yield 92%. i: NaOH, EtOH, 40 °C, 24 h; yield 77% **13**, colorless oil. j: Toluene, DIBAH, −70 °C, 12 h; yield 54% **14**, colorless oil.

Cycloaddition of the (*Z*,*E*)-1-methoxy-1,3-hexadiene **5**[5], which bears a functionalized C_2 substituent at C-4, with menthyl (−)-glyoxylate **6** affords a mixture of the pseudoglycaluronates **8**, **9**, and **10** that can be easily separated. A 1 : 1 mixture of **8** and **9** can also be obtained in good yield from the mesoxalate adduct **7**[5]. **9** is catalytically converted with boron trifluoride-ether into the α-

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anomer **10** in quantitative yield. The higher thermodynamic stability of **10** is due to the anomeric and allylic effects[6], which are effective in the $^0H_5$ conformation of **10**[7]. The compounds **9** and **10** have the necessary relative stereochemistry at C-4 and C-5. After conversion[8] into the lactone **11**, reduction with equimolar amounts of diisobutylaluminum hydride (DIBAH) at $-70\,^\circ C$ affords the lactol. After reaction with *tert*-butyl(dimethyl)silyl chloride (TBDMS-Cl), the carboxylic acid **13** is obtained by ester hydrolysis, and the aldehyde **14**—an analogue of **1**—by repeated reduction with DIBAH. The compounds **11**, **13** and, in particular, **14** are valuable intermediates for thromboxane syntheses.

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[6] See [1b] and references cited therein.
[7] $^0H_5$ conformation was also observed in the pseudoglycaluronates **8** and **12**.
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Hydroxylation of Acyclic Alkanes by Oxygen Atoms O(^{3}P)—Comparison of Ozone and O(^{3}P) Oxidations of Alkanes**

By *Elazar Zadok* and *Yehuda Mazur**

Ozone oxidation of saturated compounds leads to introduction of OH groups at tertiary positions[3]. This method is generally applicable to saturated cyclic hydrocarbons, but not to acyclic hydrocarbons which give comparatively large amounts of ketones derived from cleavage of C—C bonds[6].

Looking for an alternative method, we utilized ground state oxygen atoms (O(^{3}P) atoms) generated by low-pressure microwave discharge of a CO_2/He mixture in a flow system[2]. We have recently found that O atoms produced in this way convert saturated cyclohexane derivatives mainly into tertiary alcohols and epoxides[1].

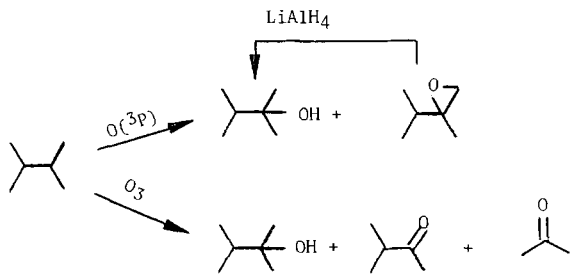
We have now applied this oxidation method to five acyclic hydrocarbons and have found that also in these cases the major products were tertiary alcohols and tertiary epoxides (Table 2). Since reduction of these epoxides with $LiAlH_4$ leads to the same tertiary alcohols, the reduction of the total mixture of products gave the alcohols in comparatively high yields. The amounts of ketones derived from C—C bond cleavage is considerably lower than in the ozone oxidation (Table 2).

Table 2. Product distribution [%] in the reaction of O(^{3}P) with acyclic hydrocarbons.

Substrate	Tertiary alcohols [a]	Secondary and primary alcohols + ketones	Epoxides	Ketones (by C—C cleavage) [b]
	64 (97)	2	34	— (65)
	55 (73)	21	20	4 (42)
	52 (75)	13	24	12 (50)
	45 (82)	15	40	— (57)
	51 (67)	32	17	— (77)

[a] In parenthesis: relative yields after reduction of reaction mixture with lithium aluminium hydride. [b] In parenthesis: relative yield of C—C cleavage products formed in the ozone oxidation.

This may be exemplified by the oxidation of 2,3-dimethylbutane, which results in 2,3-dimethyl-2-butanol (64%) and 1,2-epoxy-2,3-dimethylbutane (34%), and after reduction with lithium aluminium hydride in 97% of the tertiary alcohol (Scheme 1). Reaction of 2,3-dimethylbutane and O_3 gave only 35% of the tertiary alcohol in addition to acetone (37%) and 3-methyl-2-butanone (28%)[6].



Scheme 1.

Although both ozone and O(^{3}P) hydroxylate saturated hydrocarbons, they operate by different mechanisms. Ozonation of hydrocarbons involves electrophilic attack of O_3 on C—H bonds, leading to reversible formation of a dipolar intermediate from which alcohols (C—H cleavage) or ketones (C—C cleavage) are formed. Steric effects play an important role in the ozone oxidation and are responsible in acyclic hydrocarbons for the fact that not only C—H- but also C—C-bonds can readily be attacked.

The mechanism for the reaction of O(^{3}P) with hydrocarbons probably involves H atom abstraction to form a radical pair[1]. Radical combination in a solvent cage leads to alcohols, while disproportionation of the radicals gives olefins which are then epoxidized by O atoms. This reaction, which occurs when the O-atom is colinear with the C—H bond, has comparatively small steric demands[10] and does not differentiate between cyclic and acyclic hydrocarbons.

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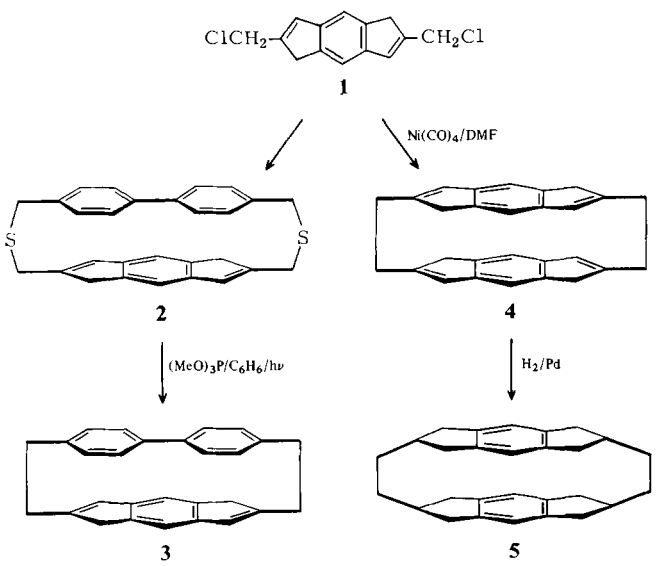
Phanes Derived from 1,5- and 1,7-Dihydro-*s*-indacene**

By *Peter Bickert, Virgil Boekelheide,* and *Klaus Hafner**

Frontier orbital analysis of two conjugated, cyclic polyenes held face-to-face in close proximity suggests that when both polyenes have $4n\pi$-electron systems the interaction will be stabilizing, whereas when both have $(4n+2)\pi$-electron systems the interaction will be destabilizing[1]. To test this prediction experimentally it would be of especial interest to examine phanes having nonbenzenoid aromatic and also antiaromatic decks as model compounds.

In the course of experiments directed toward a synthesis of [2.2](2,6)-*s*-indacenophane, we have now prepared, *inter alia*, the tetrahydro-*s*-indacenophane **4** by means of a cyclization method not previously employed in phane chemistry.

The 2,6-disubstituted dihydro-*s*-indacene, needed as a precursor for this synthesis, was prepared in a straight-forward fashion from dimethyl 2,5-bis(bromomethyl)terephthalate[2]. On reaction with diethyl malonate in the presence of excess sodium ethoxide it was converted in 85% yield into diethyl 1,5-dioxo-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylate (m.p. = 158–161 °C (dec.)), which after reduction with $NaBH_3CN$/acetic acid followed by elimination of water using TsOH/$CHCl_3$ gave diethyl 1,5-dihydro-*s*-indacene-2,6-dicarboxylate[3a] as stable colorless needles (m.p. = 186–187 °C), intensely fluorescent under long wavelength UV light. Reduction of this with diisobutylaluminum hydride gave 1,5-dihydro-*s*-indacene-2,6-dimethanol[3b] as air-sensitive, colorless crystals (m.p. = 197–199 °C (dec.)) which was converted by treatment with $SOCl_2$ into a mixture of 2,6-bis(chloromethyl)-1,5-dihydro-*s*-indacene **1** and its 1,7-dihydro isomer (m.p. = 137–140 °C (dec.)). The overall yield from the bis(β-keto ester) was 50%.



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Treatment of **1** with 4,4′-biphenyldimethanethiol under high dilution conditions gave the corresponding dithia[3](4,4′)biphenylo[3](2,6)dihydro-*s*-indacenophane **2** (colorless crystals, dec. > 250 °C)[3c], and desulfurization by irradiation in a solution of trimethyl phosphite/benzene gave the [2.2]phane **3** (colorless crystals, dec. > 250 °C) in 33% yield[3d].

Attempts to prepare tetrahydro-*s*-indacenophane **4** from **1** by standard methods of cyclophane synthesis failed. However, when **1** was treated with tetracarbonylnickel in *N,N*-dimethylformamide, following the procedure of *Corey et al.*[4] for converting allyl halides into macrocycles, the desired phane **4** was formed in 10% yield as a mixture of double bond isomers (air-sensitive, colorless crystals, dec. > 100 °C)[3e]. Catalytic hydrogenation of **4** readily gave the novel, bridged "cyclophane" **5** (colorless crystals, m.p. = 204–206 °C (dec.))[3f].

The intermediate diethyl 1,5-dioxohexahydro-*s*-indacene-2,6-dicarboxylate has also been shown to be a useful precursor for a logically-designed synthesis of 1,5- and 1,7-dihydro-*s*-indacene, interesting molecules for which there are other known literature procedures[5]. Hydrolysis and decarboxylation of the bis(β-keto ester) with TsOH/acetic acid gave tetrahydro-*s*-indacene-1,5-dione (m.p. = 230–231 °C)[3g], which on reduction with $NaBH_4$ to the corresponding 1,2,3,5,6,7-hexahydro-*s*-indacene-1,5-diol followed by dehydration using TsOH in $CHCl_3$/tetrahydrofuran gave 1,5(1,7)-dihydro-*s*-indacene in 56% overall yield.

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Active Transport of Amino Acid Anions by a Synthetic Metal-Complex Carrier

By *Hiroshi Tsukube**

Although membrane transport of amino acid anions, ATP, and other compounds has been recognized to play important roles in biology, and to have wide applications in separation science, very few artificial carriers have been reported for the selective transport of these anionic species[3,4].

Here we report that a new series of transition-metal complexes of the macrocyclic polyamine 1,4,7,10-tetrabenzyl-1,4,7,10-tetraazacyclododecane (tbcyclen) display nov-

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el, characteristic functions for the active transport of amino acid anions[6]. Advantageous are that tbcyclen is easily prepared, that its metal complexes can coordinate substrates, and that the benzyl groups of tbcyclen offer the excellent hydrophobic properties required of an effective carrier.

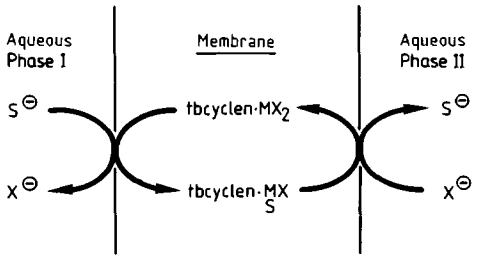

Fig. 1. Active transport of amino acid anions (substrate anion $S^{\ominus}$) through a membrane; M = metal ion, $X^{\ominus}$ = antiport anion, tbcyclen = 1,4,7,10-tetrabenzyl-1,4,7,10-tetraazacyclododecane.

Table 1 (Extract). Active transport of amino acid anions by a metal-complex carrier. Initial concentrations: Aqueous phase I: 0.250 mmol substrate in 5 mL of 0.05 N NaOH. Aqueous phase II: 0.250 mmol substrate and 5.0 mmol antiport anion salt in 5 mL of 0.05 N NaOH. Membrane: 0.056 mmol metal-complex carrier in 12 mL of $CHCl_3$.

Substrate	Antiport Anion	Equilibrated Substrate Distribution [mmol] [a]		
		Aq. Phase I	Membrane	Aq. Phase II
tbcyclen-$NiCl_2$-System				
Bz-Gly	$Cl^{\ominus}$	0.166	0.051	0.283
tbcyclen-$CoCl_2$-System				
Bz-Gly	$Cl^{\ominus}$	0.140	0.013	0.347
tbcyclen-$CuCl_2$-System				
Bz-Gly	—	0.211	0.078	0.211
Bz-Gly	$Cl^{\ominus}$	0.144	0.026	0.330
Bz-Gly	$ClO_4^{\ominus}$	0.201	0.033	0.266
Bz-Gly	$SCN^{\ominus}$	0.226	0.014	0.260
Bz-Ala	$Cl^{\ominus}$	0.057	0.006	0.437
Bz-Gly-Gly	$Cl^{\ominus}$	0.161	0.004	0.335
Bz-Glu	$Cl^{\ominus}$	0.077	0	0.423
Bz-Val	$Cl^{\ominus}$	0.105	0.040	0.355

[a] Determined spectroscopically after 24 h's experiment. Bz = benzoyl.

Some amino acids anions were effectively transported against their concentration gradients with the aid of these metal-complex carriers *via* an anion exchange mechanism[4] (Fig. 1, Table 1). The transport selectivity and efficiency of the system could be regulated by the nature of the ligand, as well as by the type of coordinated metal ion, and antiport anion:

- The novel carrier, tbcyclen-$CuCl_2$, showed different transport selectivities from those displayed by previously reported copper complexes and lipophilic organic carriers[4]. This indicates that coordination character and lipophilic properties of the ligand essentially influence the transport behavior.
- tbcyclen-$CuCl_2$ and -$CoCl_2$ were found to facilitate transport of amino acid anions more effectively than the corresponding $NiCl_2$ complex.
- The influence of the antiport anion on the transport rates clearly shows that $Cl^{\ominus}$ is more effective than $ClO_4^{\ominus}$ or $SCN^{\ominus}$ in this respect.

Hence, the metal-complex carriers discussed here may provide a simple model for biological transport as well as prototypes for the separation of anions by membranes.

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Electrochemical Reduction of [2.2]Paracyclophane

By *Rodolphe Jund, Paul Lemoine*, and *Maurice Gross**

[2.2]Paracyclophane exhibits enhanced basicity compared to other cyclophanes[6] and its reduction potential, $E_{1/2}$, which has only been determined indirectly to date (-3.05 ± 0.12 V *vs.* SCE) is, as expected, more negative than that of other cyclophanes[1]. We have now determined this potential directly using a dropping mercury electrode in the system *N,N*-dimethylformamide (DMF)/tetrabutylammonium perchlorate: $E_{1/2} = -3.00 \pm 0.05$ V *vs.* SCE. Attempts to determine the electrochemical reduction of benzene under the same conditions failed, even at $-35\,^{\circ}C$. Reduction of [2.2]paracyclophane can also be studied cyclovoltammetrically. Whereas no anodic peak is observed at low potential scan rates (5–20 V/s), at higher rates (> 50 V/s) such a peak is observed (Fig. 2). This indicates that the reduced species rapidly decomposes.

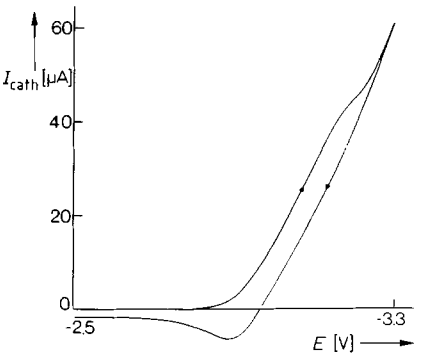

Fig. 2. Cyclovoltammogram of [2.2]paracyclophane (7×10^{-3} mol/L). Solvent DMF. Conducting salt: tetrabutylammonium perchlorate (0.2 mol/L). Electrode: mercury. Potential scanning rate: 100 V/s. Triangular sweep between -2.5 and -3.3 V (*vs.* SCE).

The number of electrons transferred in the reduction could not be determined by potentiostatic coulometry. However comparison of the height of the polarographic reduction wave of [2.2]cyclophane with those of "similar" compounds (naphthalene, phenanthrene, anthracene) suggests that the reaction is a two electron transfer process. The experimental results are certainly consistent with the hypothesis that the electrochemical reduction of [2.2]paracyclophane generates a diradical—bromination of [2.2]paracyclophane to afford 4,12-dibromo[2,2]paracyclophane is also in accord with this—but the involvement of a dianion cannot be excluded.

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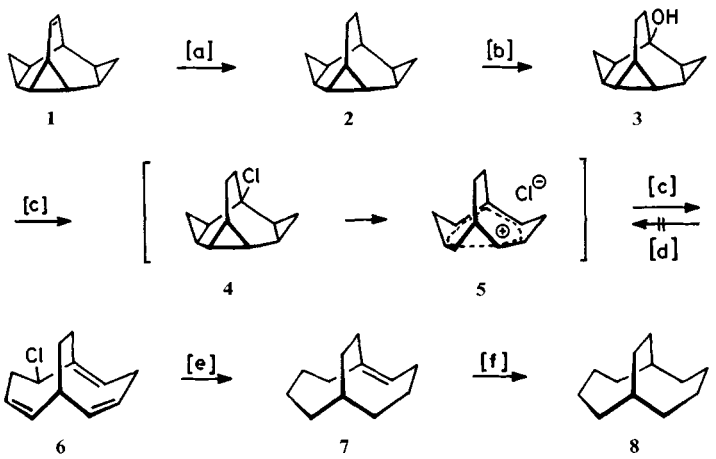
Bicyclo[4.4.2]dodeca-1-ene—The First "Hyperstable" Bridgehead Olefin**

By *Hanspeter Kukuk, Ehrhardt Proksch*, and *Armin de Meijere**

Bridgehead olefins have long lost their uniqueness[1]. On the basis of force field calculations the possible existence of "hyperstable" bridgehead olefins has recently been predicted, yet no experimental evidence of such species has so far appeared in the literature[2]. We therefore describe the surprising result of unsuccessful attempts to prepare a bridged trishomocycloheptatrienyl cation, which unexpectedly led to the formation of the hyperstable compound **7** (Scheme 1).

Catalytic hydrogenation of the *exo,exo*-bishomobullvalene **1**[3] afforded pentacyclo[4.4.2.0^{2,4}.0^{5,7}.0^{8,10}]dodecane **2**, an ethano-bridged *cis*-trishomocycloheptatriene. **2** can be oxidized to the bridgehead alcohol **3** (42% yield) by dry ozonation[4] on silica gel deactivated with 5 wt-% of potassium hydroxide. Reaction of **3** with sulfinyl chloride in the presence of diethylaminomethylpolystyrene does not lead



Scheme 1. [a] PtO_2/H_2, MeOH, RT; [b] O_3/SiO_2-KOH; [c] $SOCl_2$, polymer base, CH_2Cl_2, −40 °C to RT; [d] SbF_5, SO_2ClF, −110 to −78 °C; [e] PtO_2/H_2, Et_2O, 24 h; [f] as [e], but 72 h.

to the expected bridgehead chloride **4**, even under mild conditions (−40 to +20 °C). Rather, according to its ^{1}H- and ^{13}C-NMR spectra the product (61%) is the 10*exo*-chlorobicyclo[4.4.2]dodeca-1,4,7-triene **6** [δ(^{1}H) = 5.82 (dddd, H-5), 5.52—5.65 (m, H-2,4,7), 5.12 (dddd, H-8), 4.37 (ddd, H-10^{endo}); δ(^{13}C) = 140.5 (C-1), 5 doublets at 138.1, 131.7, 130.8, 128.8, 117.9 (C-2,4,5,7,8)].

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Obviously **4** is so labile that it rearranges in a [$_\sigma$2$_s$ + $_\sigma$2$_s$ + $_\sigma$2$_s$]-cycloreversion *via* the bridgehead cation to **6**, even in the weakly polar solvent dichloromethane. Several attempts by spectroscopic investigation to directly demonstrate the presumed intermediary formation of the bridged trishomocycloheptatrienyl cation **5** as the first representative of its kind[5] have failed. Under superacidic conditions (HSO_3F/SbF_5 or SbF_5/SO_2ClF) only polymers were obtained, both from **3** as well as from **6**.

6 is a bridgehead olefin of the hitherto little known bicyclo[4.4.2]dodecane system. Such bridgehead olefins should, according to molecular mechanics calculations, exhibit less strain energy than the corresponding saturated hydrocarbons[2]. **6** can be reductively dehalogenated over prehydrogenated platinum dioxide in ether, and selectively hydrogenated to the monoolefin **7** [δ(^{1}H) = 5.35 (br. dd, H-2); δ(^{13}C) = 142.26 (s, C-1), 126.95 (d, C-2), 10 signals between 36.84 and 24.35]. The finding that further hydrogenation to bicyclo[4.4.2]dodecane **8** requires at least three times longer reaction time, seems to indicate that there is a "hyperstability effect"[2] in **7**.

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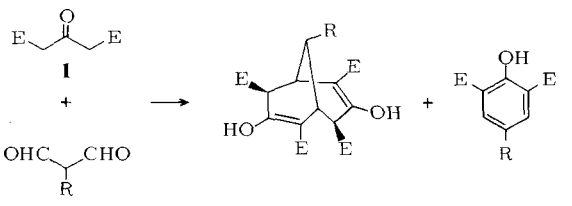
Synthesis of Bicyclo[3.3.1]nonane Derivatives under Physiological Conditions

By *Steven H. Bertz** and *Gary Dabbagh*

Prelog et al. prepared a variety of phenols from 1,3-dicarbonyl compounds and diethyl 3-oxoglutarate or ethyl acetoacetate in hot ethanolic sodium ethoxide[1a]. It has been shown that in some cases better yields can be obtained by conducting the reaction at room temperature in aqueous solution containing 0.1 to 1 equivalents of NaOH (pH 7—8) and methanol cosolvent[1b]. Organic chemists often refer to such buffered[1c] aqueous solutions as "physiological conditions"[1d]. We wish to report that when they are treated with dimethyl 3-oxoglutarate **1** under these



2, R = H
3, R = *n*-C_5H_{11}
E = CO_2CH_3

4 **5** **6** **7**

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conditions, malondialdehyde **2** and *n*-pentylmalondialdehyde **3** yield bicyclo[3.3.1]nonane derivatives **4** (67%) and **5** (21%), respectively. This new reaction is reminiscent of the formation of tropinone derivatives from 3-oxoglutarate, succindialdehyde, and methylamine[1d].

The yields of **4** and **5** fall off as the pH is raised above 8 or lowered below 7. The yield of phenol **6** obtained from **1** and **2** is maximal (43%) at pH 4.5. In contrast, the yield of phenol **7** is maximal (26%) at pH 7, which explains why the yield of **5** is lower than that of **4**. Remarkably, under *Prelog*'s conditions only **4** is produced from **1** and **2**, although the yield (49%)[2] is lower than under physiological conditions. Only 10% of **7** and no **5** is observed with **1** and **3** under these conditions. Thus, compounds **4**, **5**, and **7** are all best prepared under physiological conditions.

The preferred formation of **6** at low pH has been adduced as supporting evidence for the intermediacy of dimethyl 2-oxo-5-hydroxy-3-cyclopentene-1,3-dicarboxylate in the Weiss reaction of **1** with glyoxal at pH 5[3a]. Given the precedents[1a] for phenol formation and the driving force of aromatization, it is surprising that **1** and **2** proceed to afford **4** in analogy to the formation of bicyclo[3.3.0]octane[3b] or bicyclo[3.3.2]decene[3c] derivatives from **1** and glyoxal or *o*-phthalaldehyde, respectively. In neither of these cases is a six-membered ring intermediate possible, thus our work bridges this gap between five- and seven-membered ring compounds and clarifies when the driving force of aromatization is effective.

In order to prove the structure, **4** was hydrolyzed and decarboxylated[4a] to yield bicyclo[3.3.1]nonane-3,7-dione[4b] (83%) in what is also a very convenient preparation of this useful compound[4c]. Similarly, after hydrolysis and decarboxylation **5** furnished the novel 9-pentylbicyclo[3.3.1]nonane-3,7-dione (100%)[4d].

Ethyl 2-formyl-3-oxopropionate[5a] reacts with **1** to give only the mixed ester of 2-hydroxy-1,3,5-benzenetricarboxylic acid at pH 5 (65%) and pH 7 (70%, 78% as the Na salt). No transesterification is observed under our mild conditions. Bromomalondialdehyde gave neither phenol nor bicyclo[3.3.1] derivative at pH 5 or 7; no product was observed by *Prelog et al.* either[1a].

This new reaction furnishing bicyclo[3.3.1]nonane derivatives is significant because of the large increase in molecular complexity[5b] brought about under very mild conditions, which are not likely to affect other functional groups.

Experimental

5: Dimethyl 3-oxoglutarate (7.0 g, 0.04 mol) was dissolved in 10 mL of methanol and 10 mL of 1.0 M NaOH added, followed by 1.7 g (0.01 mol) of the sodium salt of **3**[6]. The final pH was 8. After being stirred for 4 days at ambient temperature, acidification to pH 3 gave 1.9 g of crude material, which was isolated by decanting the aqueous layer and drying the organic residue *in vacuo*. (Extraction of the aqueous layer with CH_2Cl_2 gave 4.5 g of **1**.) Crystallization from $CHCl_3$ yielded 0.95 g (21% relative to **3**). Recrystallization from $CHCl_3/CH_3OH$ (1:1) gave an analytically pure sample, m.p. = 129–131°.

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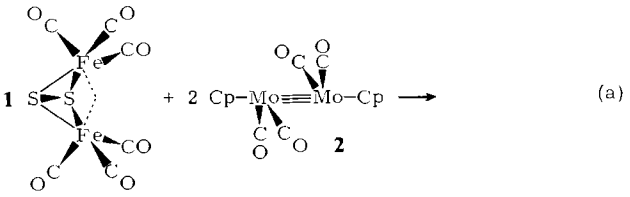
A New Type of Iron-Molybdenum-Sulfur Cluster: Synthesis and Structure of $[Fe_2Mo_2(\eta^5\text{-}C_5H_5)_2(\mu_3\text{-}S)_2(\mu_3\text{-}CO)_2(CO)_6]$**

By *Pierre Braunstein**, *Jean-Marc Jud*, *Antonio Tiripicchio*, *Marisa Tiripicchio-Camellini*, and *Enrico Sappa*

Iron-molybdenum-sulfur clusters[1] are of interest, *inter alia*, because of their occurrence in nitrogenase[2]. We have now prepared a new cluster of this type, namely **3**, with the unprecedented framework stoichiometry $\{Fe_2Mo_2S_2\}$, by reaction of the diiron complex **1**[3] with the dinuclear molybdenum compound **2** ($Cp = \eta^5\text{-}C_5H_5$) in toluene.



$$Fe_2Mo_2Cp_2(\mu_3\text{-}S)_2(\mu_3\text{-}CO)_2(CO)_6 + [CpMo(CO)_3]_2$$
3 **4**

Reaction (a) is the third example[4] for the formation of a heterotetranuclear cluster from **1** and a dinuclear species. The high reactivity of the MoMo triple bond in **2** towards electrophiles and nucleophiles[5] facilitates reaction under very mild conditions.

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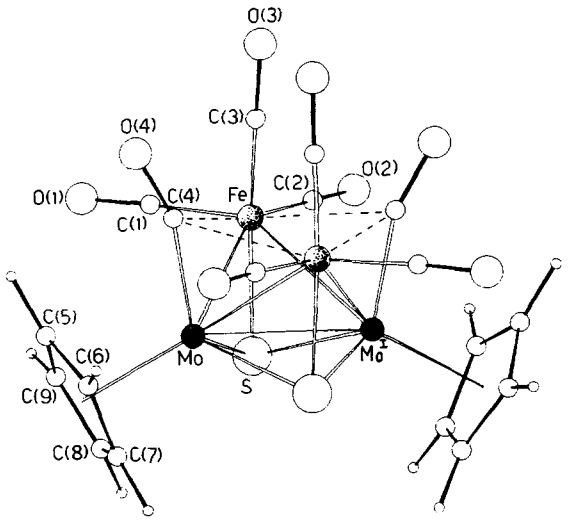

Fig. 1. Molecular structure of **3** in the crystal. C2/c; $Z=4$; $a=17.927(10)$, $b=8.316(4)$, $c=15.978(8)$ Å; $\beta=114.31(5)°$; $V=2171(2)$ Å^3, $\rho_{calc}=2.209$ g cm^{-3}; 1485 independent reflections ($3°<\theta<23°$), Nb-filtered $Mo_{K\alpha}$ radiation, 504 reflections ($I>2\sigma(I)$) were used in structure solution and refinement; $R=0.052$. Selected bond distances (Å) and angles (°): MoMo' 2.846(5), MoFe 2.818(5), MoFe' 2.815(5), MoS 2.335(9), MoS' 2.327(9), FeS 2.165(8), MoC4 1.90(4), FeC4 2.62(3), Fe'C4 2.64(3); FeMoFe' 85.8(1), FeMoMo' 59.6(1), FeMo'Mo 59.7(1), MoFeMo' 60.7(1), MoSMo' 75.3(3), FeSMo 77.4(3), FeSMo' 77.5(3), MoC4O4 159(3), FeC4O4 119(2), Fe'C4O4 116(2). I indicates the transformation $-x, y, 1/2-z$. **3** has forced C_2-symmetry, but it is almost C_{2v}.

The X-ray structure analysis of **3** (Fig. 1) (cf. [6a]) revealed a "butterfly arrangement" of the four metal atoms with the two molybdenum atoms in the hinge position (butterfly angle: 104.1°). A four-electron donor sulfur atom is μ_3-bonded on each $FeMo_2$ wing, confirming the tendency of sulfido-ligands to assist cluster formation[1b, 3b]. Noteworthy is the unusual nature of the two CO-bridges. The IR spectrum suggests presence of μ_3-bonding [ν(CO) (KBr): 2043 m, 2010 s, 1982 s, 1975 s, 1956 m, *1791* ms cm^{-1}], but this situation usually occurs for CO ligands capping a closed trimetallic face, whereas the arrangement of $MoFe_2$ is open (Fe···Fe' = 3.833(5) Å).

One can visualize the formation of **3** as a formal "insertion" of the MoMo triple bond of **2** into the Fe_2S_2 core of **1** accompanied by Fe—Fe and S—S bond breaking. This would reduce the metal-metal bond order; the Mo—Mo distance in **3** (2.846 Å) is indeed intermediate between that in **2** (2.448 Å[6b]) and in **4** (3.235 Å[6c]).

Experimental

All reactions and operations were carried out under nitrogen. Solvents were dried and distilled under nitrogen before use. A solution of **1**[6d] (0.47 g, 1.4 mmol) in toluene (25 ml) was added at 0°C to a solution of **2**[5a] (1.20 g, 2.8 mmol) in the same solvent (75 ml). This mixture was stirred for 0.25 h at 0°C. The residue obtained after filtration and evaporation under reduced pressure was chromatographed on a silica gel column. Elution with pentane gave a red-brown solution of $Fe_3S_2(CO)_9$ (0.03 g). Further elution with toluene/pentane (3:10) furnished a red solution of **4** [0.25 g (0.5 mmol) ≙ 21% based on Mo, after recrystallization from CH_2Cl_2/pentane]. Using a toluene/pentane (1:1) eluent afforded a red-brown solution of **3**, from which dark-red monoclinic crystals were obtained with CH_2Cl_2/pentane [0.325 g ≙ 33% based on Fe; m.p. > 140°C (decomp.)]. Elution with THF afforded a dark-brown compound which has not yet been characterized.

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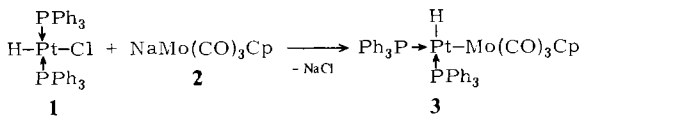
Synthesis and Structure of a Heterodimetallic Complex Containing a Terminal Hydrido Ligand: $[(PPh_3)_2(H)PtMo(CO)_3(\eta^5\text{-}C_5H_5)]$**

By *Odile Bars* and *Pierre Braunstein**

Dinuclear hydridocarbonyl complexes are considered to be interesting model compounds or intermediates in CO reduction, and much work is presently directed towards the synthesis and characterization of such systems[1].

We have envisaged synthesizing such complexes by reaction of *trans*-$PtH(Cl)(PPh_3)_2$ **1** with carbonylmetalates. Simple chloride exchange would indeed afford the desired product, but, in view of our previous results in the field[2], more complicated pathways cannot be ruled out. Thus it was open to speculation whether the phosphane ligands in (**1**) would remain coordinated or not to the platinum during the envisaged reaction.

In the reaction of **1** with **2** we were able to isolate the complex **3** ($Cp=\eta^5\text{-}C_5H_5$).



3, IR (KBr): ν(PtH): 2103 m, ν(CO): 1916 s, 1828 s, 1797 vs cm^{-1}; ^{1}H-NMR ([D$_8$]toluene, −40°C): $\delta=-5.73$ [d, H1, ^2J(H1,P2) = 170 Hz, ^1J(Pt,H1) = 678 Hz]; 5.44 [s, 5H, Cp]; ^{31}P[^{1}H]-NMR ([D$_8$]THF, −40°C); $\delta=31.9$ [d, P1, ^2J(P1,P2) = 6 Hz, ^1J(Pt,P1) = 3690 Hz], 35.5 [d, P2, ^1J(Pt, P2) = 2653 Hz].

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The $^{31}P\{^1H\}$-NMR spectrum of the two non-equivalent phosphorus atoms appears as an AB pattern; the magnitude of $^2J(P1,P2)$ indicates a *cis*-type of orientation of the phosphane ligands. The ^1H-NMR spectrum in the hydride region shows a doublet with ^{195}Pt-satellites, thus indicating a Pt-bonded hydrido ligand in a terminal position (because of the high $\nu(Pt—H)$ frequency). The fact that $^2J(P1,H)=0$ was confirmed ^{31}P-NMR spectroscopically by an off resonance experiment.

From the NMR spectra it follows that a dynamic behavior occurs above 0 °C, and is being further investigated.

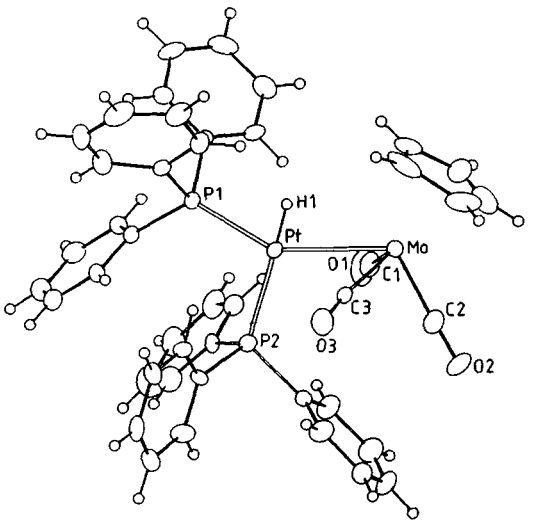

Fig. 1. Molecular structure of **3** in the crystal. $P2_1/n$, $Z=4$; $a=15.42(1)$, $b=16.44(1)$, $c=16.50(2)$ Å; $\beta=103.13(5)°$; $V=4076$ Å^3, 4159 reflections ($I>3\sigma(I)$), $Mo_{K\alpha}$ radiation, $R=0.053$. Selected bond distances [Å] and angles [°]: PtMo: 2.839(1), PtP1: 2.264(3), PtP2: 2.355(3); MoPtP1: 149.1(1), MoPtP2: 108.8(1), P1PtP2: 101.3(1).

According to the X-ray structural analysis of **3** (Fig. 1) the Pt atom is located in the plane defined by P1, P2 and Mo, but the usual square-planar environment found for Pt[1] complexes is strongly distorted in order to minimize steric repulsions between the bulky groups. The terminal hydride could not be located on the Fourier difference map and H1 was placed at 1.6 Å from Pt[3] on the bisector of the large P1—Pt—Mo angle, leading to a P2—Pt—H1 angle of 183.4°. The Pt—Mo distance in **3** appears to be the first value of its kind reported for such a bond in a bimetallic complex[4] and is intermediate between the value 2.889 Å found in the trimetallic carbene complex[5] *trans*-$Pt(C_6H_{11}NC)[(C_6H_{11}NH)C(OC_2H_5)][Mo(CO)_3Cp]_2$ and of 2.813 Å (average value) in the tetrametallic cluster[2a] $Pt_2Mo_2Cp_2(CO)_6(PEt_3)_2$.

Experimental

All reactions and operations were carried out under nitrogen. Solvents were dried and distilled under nitrogen before use. To a suspension of **1** (1.89 g, 2.5 mmol) in THF (20 ml) at −40 °C was added a THF solution (30 ml) of **2**, prepared from $[Mo(CO)_3Cp]_2$ (0.613 g, 1.25 mmol). When the reaction temperature was slowly raised to 0 °C, the solution turned red. The reaction mixture was stirred for 1 h at 0 °C and then filtered to remove NaCl. An equal volume of pentane was added to this solution and after cooling to −20 °C, an orange powder precipitated which was recrystallized from toluene/pentane, affording orange crystals of the product **3** [yield 1.0 g, 41.4% based on Pt; m.p. 158 °C (decomp.)].

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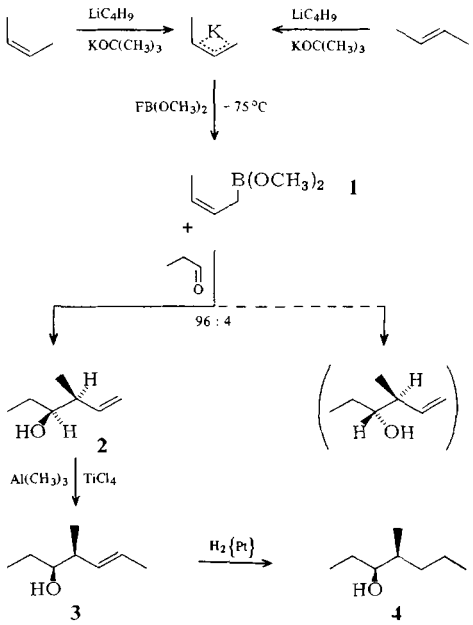
A Stereocontrolled Synthesis of the Pheromone 4-Methyl-3-heptanol: Novel and Selective CC-Linking Reactions**

By *Manfred Schlosser** and *Katsuramaru Fujita*

Dedicated to Professor Herbert Grünewald on the occasion of his 60th birthday

The (*S,S*)-enantiomer of 4-methyl-3-heptanol is the major constituent of the aggregation pheromone of the elm bark beetle *Scolytus multistriatus* Marsham[2]. The synthesis of the racemate described here illustrates the utility of two novel, stereoselective methods for CC-linking: Addition of dimethyl (*Z*)-2-alkeneboronates to aldehydes, and transfer of alkyl groups to olefinic double bonds with titanium reagents.

After torsional isomerization in tetrahydrofuran (THF) 2-butenylpotassium assumes the (*Z*)-configuration (*"endo"* form) to the extent of more than 99%[3b]. Condensation with fluorodimethoxyborane at −75 °C affords almost pure dimethyl (*Z*)-2-buteneboronate **1**[4]. This reacts as ex-



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pected[5] with propanal to give the *"erythro"*-4-methyl-5-hexen-3-ol **2**, the adduct having the (*R**,*R**)-configuration. The reaction proceeds rapidly (1 h at −75 °C, 30 min at 25 °C), stereoselectively (*erythro*/*threo*-ratio between 95 : 5 and 99 : 1, depending on the temperature profile), and with satisfactory yields (>60%). Thus, their is no need for the alternatively proposed indirect route[5c] *via* 2-butenylbis(dimethylamino)borane and 2-(2-butenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

For chain-extension, **2** is dissolved in THF and treated with trimethylaluminum (or methyllithium) and titanium tetrachloride (molar ratio 1 : 2 : 1). After 30 min at 0 °C, the solvent is removed by distillation under nitrogen and the residue heated to 120 °C for 3 h. Subsequent hydrolysis affords *"erythro"*-(5*E*)-4-methyl-5-hepten-3-ol **3** (b.p. 67–69 °C/15 torr) as sole volatile product (32%), besides traces of unreacted **2**. Catalytic hydrogenation of **3** leads quantitatively to the pheromone constituent 4-methyl-3-heptanol **4** (b.p. 51–54 °C/15 torr).

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Evidence for Intermediates in the Cycloaddition of Singlet Carbenes**

By *Bernd Giese**, *Woo-Bung Lee*, and *Carola Neumann*

Singlet carbenes have a vacant p-orbital and an occupied σ-orbital. Cycloadditions with alkenes therefore depend upon electrophilic properties (p/π-interaction) and nucleophilic properties (σ/π* interaction) of the carbenes[1]. Because of the smaller energy difference between the interacting orbitals[1] in reactions of CBr_2 and CCl_2 the electrophilic p/π interaction is greater than the nucleophilic σ/π* interaction. Substituents on the alkene which raise the energy of the π orbital increase the p/π interaction and should therefore lower the activation energy of the cycloaddition. This is not the case, however, as the data determined in competition experiments show (see Table 1).

Table 1. Influence of varying the substituents in 2-methylpropene (R = CH_3) on the activation enthalpies [kJ·mol^{-1}] and activation entropies [J·mol^{-1} s^{-1}] of cycloadditions with CBr_2 and CCl_2.

Alkene	CBr_2		CCl_2	
	$\Delta\Delta H^{\neq}$	$\Delta\Delta S^{\neq}$	$\Delta\Delta H^{\neq}$	$\Delta\Delta S^{\neq}$
$CH_3CR{=}CH_2$	≡ 0.0	≡ 0.0	≡ 0.0	≡ 0.0
$CH_3OCR{=}CH_2$	2.5	17	2.0	16
$C_6H_5CR{=}CH_2$	3.4	14	2.6	13
$CH_3CR{=}CHCH_3$	5.8	26	0.3	11
$CH_3CR{=}C(CH_3)_2$	10	47	1.2	22
$C_2H_5CR{=}CH_2$	0.0	− 0.4	0.0	− 1.0
i-$C_3H_7CR{=}CH_2$	0.2	− 9.2	3.3	− 0.5

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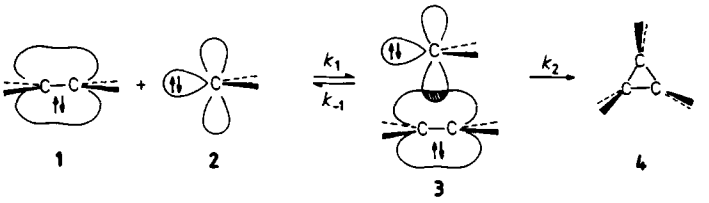
Methyl, methoxy, and phenyl groups on the alkene increase the activation enthalpies of the cycloadditions of CCl_2 and CBr_2. This cannot be explained by steric effects, because the activation enthalpies of the CBr_2 cycloadditions remain unchanged on replacing a methyl group by an ethyl or isopropyl group on the alkene (Table 1). Therefore, the substituent effects show that the nucleophilic σ/π* interaction plays a decisive role in the cycloadditions of the electrophilic carbenes CBr_2 and CCl_2. This contradiction is resolved if an intermediate **3** is postulated for the reaction of the alkene **1** with the carbene **2**[2].



In the case of a rapid equilibrium **1** + **2** ⇌ **3** the experimentally determined activation enthalpy $\Delta H^{\neq}_{exp}$ is equal to the reaction enthalpy ΔH^0 of complex formation and the activation enthalpy of the nucleophilic reaction step:

$$\Delta H^{\neq}_{exp} = \Delta H^0 + \Delta H^{\neq}_2$$

Methyl and methoxy substituents raise the energy of the π* orbitals, whereby the σ/π* distance increases and hence also the activation enthalpy $\Delta H^{\neq}_2$. Evidently for cycloadditions of CCl_2 and CBr_2 this effect is more significant than the influence of substituents on the equilibrium **1** + **2** ⇌ **3**.

The increase in reaction rate of the alkene due to methyl, methoxy, or phenyl substituents[3] is thus effected *via* an increase in the activation entropies[4].

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Synthesis, Structure, and Reactions of Primary Adducts of Sulfur or Selenium with Hexaphenylcarbodiphosphorane**

By *Hubert Schmidbaur**, *Christian E. Zybill*, and *Dietmar Neugebauer*

Double ylides of the carbodiphosphorane[3] type afford preparatively versatile phosphacumulene ylides as secondary products upon reaction with sulfur[4]:

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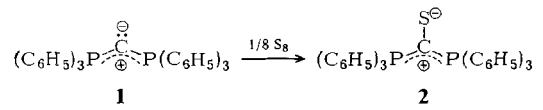
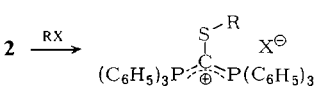
$$R_3P{=}C{=}PR_3 \xrightarrow{S_8} 2\ R_3P{=}S + CS_2 \xrightarrow{R_3P=C=PR_3} R_3P{=}C{=}C{=}S$$

Using particularly mild conditions we have now been able to show, using hexaphenylcarbodiphosphorane **1** as example, that this reaction proceeds *via* an isolable primary adduct **2** in which the carbanionic center of the ylide bonds as a donor to a sulfur atom.



1 **2**

2 forms from the components in tetrahydrofuran at $-50\,^{\circ}C$ in almost quantitative yield as a red solid, which decomposes at room temperature. Because of the strongly nucleophilic thiolate functionality, **2** reacts with methyl fluorosulfonate, benzyl chloride, or chlorotrimethylstannane to yield the colorless salts **3a–c**.

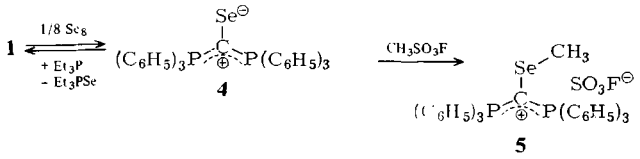


3a: R = CH_3, X = SO_3F
3b: R = $CH_2C_6H_5$, X = Cl
3c: R = $Sn(CH_3)_3$, X = Cl

2 is desulfurized by triethylphosphane at $-15\,^{\circ}C$ to reform **1**:

$$2 + P(C_2H_5)_3 \rightarrow 1 + (C_2H_5)_3P{=}S$$

Addition of selenium to the ylide **1** proceeds quantitatively, even at $-15\,^{\circ}C$, in an analogous manner to formation of **2** and affords a stable red product **4**, whose structure could be determined by single-crystal diffraction studies (Fig. 1).



4 **5**

The P=C=P framework of **1** changes only slightly on incorporation of the Se atom: the P=C bond lengths (162.9(5) or 163.8(5), depending on the modification) are lengthened to only 169.4(12) and 170.2(12) pm, and consequently the multiple bonding character remains intact. The PCP angle (130.1(6), 131.7(3) or 143.8(6)° in **1**)[5] amounts to 135.9(7)° in **4**.

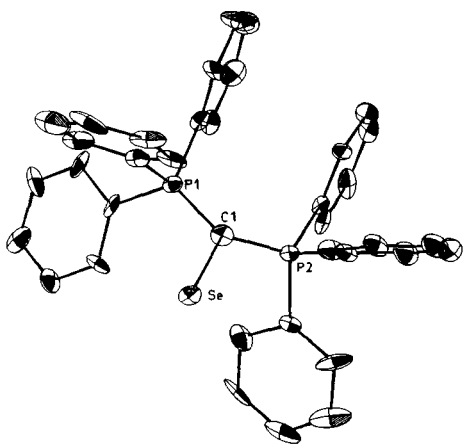


Fig. 1. Molecular structure of the selenium adduct **4** in the crystal.

The C—Se bond length (199.0(11) pm) signifies loose bonding of the selenium[6], yet the ylide carbon atom has a planar configuration (sum of angles 360°). These results clearly indicate that in carbodiphosphoranes the electron distribution and structure[5,7] can best be expressed as in formula **1**.

The selenium addition can be reversed using $(C_2H_5)_3P$. Methylation of **4** with CH_3SO_3F yields **5**.

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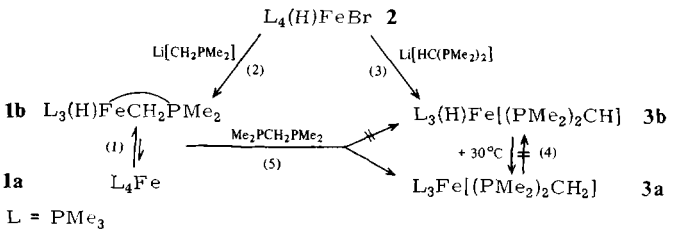
The complete manuscript of this communication appears in: *Angew. Chem. Suppl. 1982*, 590–605

[3] H. Schmidbaur, *Nachr. Chem. Tech. Lab. 27* (1979) 620.
[4] H. J. Bestmann, *Angew. Chem. 89* (1977) 361; *Angew. Chem. Int. Ed. Engl. 16* (1977) 349; *ACS Symp. Ser. 171* (1981) 25.
[5] A. T. Vincent, P. J. Wheatley, *J. Chem. Soc. Dalton Trans. 1972*, 617; G. E. Hardy, J. I. Zink, W. C. Kaska, J. C. Baldwin, *J. Am. Chem. Soc. 100* (1978) 8001.
[6] C. Matz, R. Mattes, *Z. Naturforsch. B 33* (1981) 461.
[7] U. Schubert, C. Kappenstein, B. Milewski-Mahrla, H. Schmidbaur, *Chem. Ber. 114* (1981) 3070; E. A. V. Ebsworth, T. E. Fraser, D. W. H. Rankin, O. Gasser, H. Schmidbaur, *ibid. 110* (1977) 3508; H. Schmidbaur, G. Hasslberger, U. Deschler, U. Schubert, C. Kappenstein, A. Frank, *Angew. Chem. 91* (1979) 437; *Angew. Chem. Int. Ed. Engl. 18* (1979) 408; H. Schmidbaur, T. Costa, B. Milewski-Mahrla, U. Schubert, *ibid. 92* (1980) 557; *19* (1980) 555.

A Pentakis(phosphane)iron(0) Complex by Reductive Elimination**

By *Hans Heinz Karsch**

Earlier investigations[1a,c] on complex formation in the trimethylphosphaneiron(0) system showed that a spontaneous C—H cleavage leads to an equilibrium (1) between the Fe^0- and Fe^{II}-complexes **1a** and **1b**. This reaction proceeds intramolecularly, at least in the presence of an excess of phosphane[1a]. In solution the equilibrium (1) is largely on the side of **1b**, in the solid state only **1b** is present. We have now found that **1** can also be prepared from the Fe^{II}-complex **2**[1b] *via* path (2).



In an analogous way $[(D_3C)_3P]_4Fe(D)I$ **2'**[2a] can be converted into $[(D_3C)_3P]_4(D)FeCH_2PMe_2$ **1'** in Et_2O at $-30\,^{\circ}C$. The IR spectrum (Nujol solution, 20 °C) of **1'** initially shows only one ν(Fe—D) band, but after *ca.* 30 min it also shows a ν(Fe—H) band[1a] with rapidly increasing intensity as a result of exchange according to Eq. (1). Thus, we have the first proof of such a "cyclometalation equilibrium" as an intramolecular process.

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Furthermore, **1** in combination with $Me_2PCH_2PMe_2$ serves as an ideal model system for investigating various influences on such cyclometalation reactions.

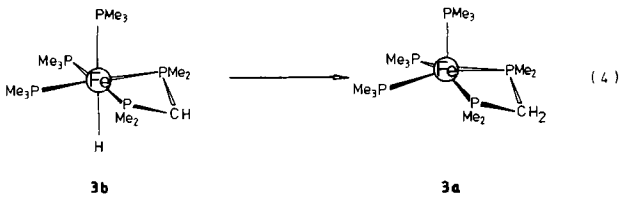
2 reacts with lithium bis(dimethylphosphino)methanide according to route (3) to give the pentakis(phosphane)iron(II) complex **3b**[2b], which, in contrast to **1b**, is unstable; it rearranges irreversibly (rapidly on warming) into **3a**[2c]. Such a reductive elimination, with the additional attribute that an atom (*i.e.* the methanide carbon) not directly bonded to the metal takes over the leaving ligand, has so far not been reported. The reverse reaction, namely the metalation of complexed methylenebis(diorganophosphane), on the other hand, is well known[3]. Other than in the case of **1**, with **3** the Fe^0 complex is favored (the proportion of which, increases with increasing temperature, in the case of **1**).

Since, according to

$$Me_2PCH_2PMe_2 + Li[CH_2PMe_2] \rightarrow Li[HC(PMe_2)_2] + PMe_3$$

PMe_3 is less acidic than $Me_2PCH_2PMe_2$ it is clear that not the acidic character (stability of the anion) is decisive for a C—H cleavage, but—e.g. in the case of **1a** (cf. [3])—the coordinatively unsaturated character. $Me_2PCH_2PMe_2$ is less space-demanding than two PMe_3 ligands and is therefore more effective for coordinative saturation (according to IR studies on corresponding $L_2Cr(CO)_4$ complexes electronic effects are not decisive). The few pentakis(organophosphane)iron(0) complexes previously described in the literature have *two* (likewise sterically favorable) $Me_2PCH_2CH_2PMe_2$ ligands[4].

Thus, **3a**, which is also accessible *via* route (5), is the first such complex with three monodentate organophosphane ligands. In solution (−90 °C) it is fluxional, in the crystalline state it has a square-pyramidal structure[5], which also distinguishes it from other P_5Fe^0 complexes[1a,c] and possibly facilitates the rearrangement (4).



(4)

3b **3a**

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[1] a) H. H. Karsch, H.-F. Klein, H. Schmidbaur, *Chem. Ber. 110* (1977) 2200; b) H. H. Karsch, *ibid. 110* (1977) 2222; c) T. V. Harris, J. W. Rathke, E. L. Muetterties, *J. Am. Chem. Soc. 100* (1978) 6966.

[2] a) Prepared from $[(D_3C)_3P]_4Fe$ and DCl/NaI in tetrahydrofuran (cf. [1a, b]): dark red crystals, ν(Fe—D) 1291 cm^{-1};—b) yellow crystals, dec. >65 °C, ν(Fe—H) 1845 cm^{-1}, ^{1}H-NMR (C_6D_6, 20 °C): δFeH = −12.4 d × quin [$_{cis}J$(P$_4$FeH) = 59, $_{trans}J$(PFeH) = 26 Hz];—c) dark-red crystals, dec. >83 °C, ^{1}H-NMR (C_6D_6, 20 °C): $\delta PCH_3 = +1.25$ "t" (N = 7.8) and 1.19 "m" (N = 5.0), $\delta PCH_2 = +2.68$ t × q (11.7 and 1.0), ^{31}P{^{1}H}-NMR: $\delta = -22.20$ q, +13.32 t (18.3 Hz).

[3] H. H. Karsch, D. Neugebauer, *Angew. Chem. 94* (1982) 322; *Angew. Chem. Int. Ed. Engl. 21* (1982) 312, and references cited therein.

[4] C. A. Tolman, S. D. Ittel, A. D. English, J. P. Jesson, *J. Am. Chem. Soc. 101* (1979) 1742.

[5] From the cell parameters (tetragonal, Laue group 4, $a = b = 796$, $c = 920$ pm, $Z = 1$, no systematic absences) it follows that the Fe atom is localized on a tetradentate axis of rotation; this requires ligand disorder: U. Schubert, private communication.

Ring Contraction 6—5/3 by Oxidative Addition to a Ferrabicycle having Novel Structural Units**

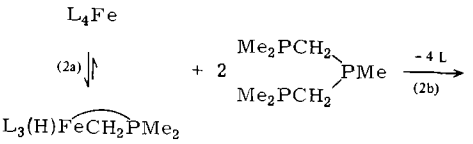
By *Hans Heinz Karsch** and *Dietmar Neugebauer*

To our knowledge cyclometalation reactions with ring contractions of type (1) have so far never been reported in the literature.

(1)

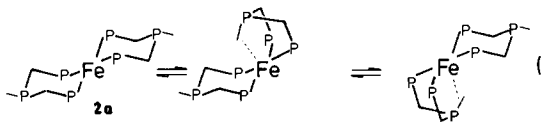
We have now been able to isolate an iron complex whose mode of formation, spectroscopic data[1], and X-ray structure analysis affords evidence of such a type of reaction.

Ligand exchange with $(Me_2PCH_2)_2PMe$[2] at the iron(0) complex **1a**, which is in equilibrium (2a) with its hydridoiron(II) isomer **1b**, leads *via* route (2b) to the product **2**.



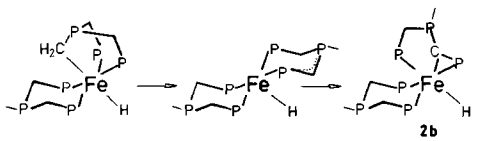
L = PMe_3 "$[MeP(CH_2PMe_2)_2]_2Fe$" **2**

Since the complex **2a** analogous to **1a** should, as coordinatively unsaturated Fe^0 compound, have an adequately long lifetime (flexible chelate angle, shielding by "free" phosphorus at position 4) to enable cleavage of C—H, *e.g.*



(3)

via equilibrium (3), it is not surprising that such an oxidative C—H addition actually occurs at the Fe center. Surprisingly, however, the primary product of this reaction is not isolated, but, due to increased CH acidity in the six-membered ring, a "diphosphinomethanide" moiety is formed in a (presumably intramolecular) acid-base secondary reaction (4)[3,4].



(4)

Of the novel structural moieties in **2b**—a six-membered M—PCPCP ring and a five-membered M—CPCP ring with annelated three-membered M—CP ring—the carbon atoms of the two smaller rings are disordered in the crystal and the positional parameters of the dotted atoms in Figure 1 could not be determined accurately.

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

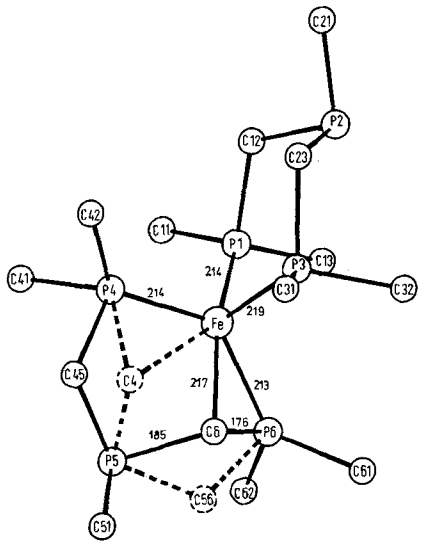
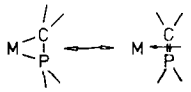


Fig. 1. Molecular structure of **2b**; the hydrido ligand could not be located with certainty. Ratio in the crystal: dotted/undotted = 2:3. Monoclinic, $P2_1/n$, $Z=4$, $a=935.9(6)$, $b=1625.8(10)$, $c=1552.1(8)$ pm, $\beta=94.69(5)°$, $V=2353.7\times10^6$ pm^3, $\rho_{calc}=1.26$ g/cm^3, $C_{14}H_{38}FeP_6$. 2116 structural factors ($F>4.5\sigma_F$; $2°\leq2\theta\leq48°$), $Mo_{K\alpha}$ ($\lambda=71.069$ pm, graphite monochromator), $R_1=0.115$, $R_2=0.118$ (Syntex $P2_1$/XTL).

The six-membered ring has chair conformation, and also the five-membered ring is not planar (P5 and C45 lie 117 and 12 pm respectively above the Fe—P4—C6 plane). The three-membered ring is oriented at an angle of 154.6° to this plane. The short P6—C6 distance favors a bonding description



which would reduce ring strain and explain the high tendency for formation of M—CP three-membered rings, and also suggests an analogy to η^1,η^2-alk-4-enyl complexes[5]. In contrast, the Fe—C6 and Fe—P4 bond lengths are "normal" for sp^3 bonds[4]. More meaningful from a coordination-chemical point of view is formulation as a 5/3 ring system. The NMR data indicate a *cis*-H—Fe—C arrangement with a phosphorus atom *trans* to an H-atom, which would allow **2b** to be termed an analogue of **1b**, despite its unusual mode of bonding and properties.

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[1] **2** crystallizes from a solution of **1** on addition of $(Me_2PCH_2)PMe$ in a very small amount of pentane (7 d, 25 °C); drying in a vacuum. Orange crystals, decomp. >115 °C; IR (Nujol): 1820 (νFe—H), 882, 453 cm^{-1} (Fe—C—P); MS: $m/z=448$ (M^+); ^{1}H-NMR (C_6D_6, 20 °C): δFeCH = −0.38 m, δFeH = −12.95 "q" × d; ^{31}P{^{1}H}-NMR: $\delta P_{complex}$ = +41.9/+39:6/+27.9/+14.0 m (b) (4P) δP_{free} = −48.5/−52.3 m "t" (2P).

[2] H. H. Karsch, *Z. Naturforsch. B37* (1982) 284.
[3] Less favorable, but not unlikely, is a "direct" C—H cleavage at the methylene carbon of the six-membered ring, which could immediately lead to **2b**. Cf. H. H. Karsch, *Angew. Chem. 94* (1982) 322; *Angew. Chem. Int. Ed. Engl. 21* (1982) 311.
[4] Cf. G. Dawkins, M. Green, J. C. Jeffery, F. G. A. Stone, *J. Chem. Soc. Chem. Commun. 1980*, 1120.
[5] H. Lehmkuhl, A. Rufinska, R. Benn, G. Schroth, R. Mynott, *J. Organomet. Chem. 188* (1980) C36; and references cited therein.

BOOK REVIEWS

Comprehensive Treatise of Electrochemistry. Vol. 2: Electrochemical Processing Edited by *J. O'M. Bockris, B. E. Conway, E. Yeager,* and *R. E. White*. Plenum Press, New York, 1981. xxii, 616 pp., bound, $ 57.50.

This is the second in a series of four volumes[*] dealing with applied or industrial electrochemistry. In the space of eleven chapters, nineteen authors attempt to describe the most important industrial processes with an electrochemical basis. The individual contributions are as follows: 1) Electrolytic Production of Hydrogen (104 pp., 133 refs.), by *B. V. Tilak, P. W. T. Lu, J. E. Colman,* and *S. Srinivasan*; 2) Production of Chlorine (62 pp., 118 refs.), by *D. L. Caldwell*; 3) Inorganic Electrosynthesis (84 pp., 371 refs.), by *N. Ibl* and *H. Vogt*; 4) Electro-Organic Syntheses (49 pp., 99 refs.), by *K. Köster* and *H. Wendt*; 5) Electrometallurgy of Aluminum (25 pp., 79 refs.), by *W. E. Haupin* and *W. B. Frank*; 6) Electrolytic Refining and Winning of Metals (54 pp., 77 refs.), by *V. A. Ettel* and *B. V. Tilak*; 7) Electroplating (17 pp., 34 refs.), by *C. J. Raub;* 8) Electrochemical Machining (122 pp., 370 refs.), by *J. P. Hoare* and *M. A. LaBoda*; 9) Theory of the Structure of Ionomeric Membranes (15 pp., 15 refs.), by *A. J. Hopfinger* and *K. A. Mauritz*; 10) Electrodeposition of Paint (33 pp., 123 refs.), by *F. Beck,* and 11) Mineral Flotation (25 pp., 60 refs.), by *R. Woods*.

It is a wide field, ranging from the electrosynthesis of inorganic and organic substances to specific industrial processes with an electrochemical basis, such as mineral flotation. Quite correctly, the currently most important electrochemical winning processes (of chlorine and aluminum), and hydrogen production, which may well be important in the future, have whole chapters devoted to them. The contributors are authorities in their fields, and the editors deserve credit for the fact that, despite the large numbers of authors and contributions, they managed to produce a homogeneous work. Virtually all the chapters begin with an introduction to the problem and economic significance of the process, follow this with a brief survey of the thermodynamic and kinetic aspects, and finally give practical solutions.

The book contains a wealth of technical details, exact numerical data, and references which will certainly make it a useful reference work for the subject specialist; at the same time, it is this very wealth of technical detail (*e.g.* plant dimensions) that will divert the newcomer from the essentials. Overall, the work is a success; one limited criticism is that it has missed the chance of consciously establishing the relationships with fundamental electrochemical problems, or making a stronger link with Volume 1 of the series. The opportunities were surely there; we have only to think of the chapter on metal winning and refining. Relating this to the corresponding problems in basic research (*e.g.* adsorption, nucleation, overvoltage, undervoltage deposition) would have opened the eyes of both the electrochemist working in basic research and the student to the problems of industrial electrochemistry. Nevertheless, the book gives an interesting insight into the problems of electrochemistry, even to those not directly concerned.

[*] *Angew. Chem. 93* (1981) 840; *Angew. Chem. Int. Ed. Engl. 20* (1981) 817.

Like Volume 1, Volume 2 is distinguished by excellent layout and painstaking typography. The extensive use of photographs and drawings is a great help in the clarification of practical aspects. This second volume can also be highly recommended to libraries specializing in this area as an enrichment of the electrochemical literature.

Dieter M. Kolb [NB 558 IE]

Liquid Phase High Pressure Chemistry. By *N. S. Isaacs*. J. Wiley & Sons, Chichester 1981. vii, 414 pp., bound, £ 33.00.

As the author explains in his preface, this is not a book for the specialist but rather for someone interested in becoming better acquainted with the details and application of a technique that is not too widely known. In this aim the author has been completely successful. In six chapters the reader is presented with a readily understandable survey on high-pressure chemistry in the liquid phase.

The author starts by describing the methods used to produce and measure high pressures, including many valuable characteristic materials data and tips on the construction of high-pressure equipment. This is supplemented by an instructively and abundantly illustrated description of selected high-pressure equipment for different analytical techniques as described in the literature.

The chemists and physicists engaged in practical work will find useful data on materials, *e.g.* compressibilities and pressure coefficients of optical and electrical properties, collected together or derived in Chapter 2.

Logically, it is only after providing this helpful material that the author turns to describe the influence of high pressures on chemical equilibria and reactions. The examples are drawn predominantly from the realm of organic chemistry, reflecting both the many organic systems that have been studied and the author's own interests. Isaacs succeeds in providing a critical appraisal of the molecular interpretation of volume effects, and also the use of these parameters derived from the pressure dependence in the discussion of mechanisms.

The increasing use of high-pressure techniques to study biochemical systems is acknowledged; this is discussed in a separate chapter. The survey is rounded off by the description of pressure effects on photophysical and photochemical phenomena.

More than 1200 literature references give an opportunity to check on details.

It is a pity that the book probably will not reach a wide circle of readers—including students—because of its high price.

Hartwig Kelm [NB 559 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 (Federal Republic of Germany).

Metal Ions in Biological Systems. Vol. 12. Edited by *H. Sigel*. Marcel Dekker, Basel 1981. xx, 353 pp., bound, SFr 165.00.—ISBN 0-8247-1429-6

Springer Series in Synergetics. Vol. 11. Chaos and Order in Nature. Edited by *H. Haken*. Springer-Verlag, Berlin 1981. viii, 275 pp., bound, DM 60.00.—ISBN 3-540-11101-8

Topics in Current Physics 26. Crystal Cohesion and Conformational Energies. Edited by R. M. Metzger. Springer-Verlag, Berlin 1981. xi, 154 pp., bound, DM 54.00.—ISBN 3-540-10520-4

Organische Leiter, Halbleiter und Photoleiter. By *C. Hamann, J. Heim*, and *H. Burghardt*. Verlag Friedr. Vieweg & Sohn, Braunschweig 1981. 195 pp., bound, DM 24.00.—ISBN 3-528-06861-2

Cellular Immunology: Selected Readings and Critical Commentary. Edited by *V. L. Sato* and *M. L. Gefter*. Addison-Wesley, Reading, Massachusetts 1981. xiv, 647 pp., bound, $ 21.50.—ISBN 0-201-10434-2

Progress in Analytical Atomic Spectroscopy. Vol. 3. Edited by *C. L. Chakrabarti*. Pergamon Press, New York 1981. v, 390 pp., bound, $ 105.00.—ISBN 0-08-029081-7

Korrosionsschutz von Stahlbauten durch Beschichtungen und Überzüge.—Die neue DIN 55928.—By *K.-A. van Oeteren*. Verlag F. H. Kleffmann GmbH, Bochum 1981. 35 pp., brochured, DM 14.00.—ISBN 3-446-12547-7

Chemische Energetik. By *W. Weber*. Aulis Verlag Deubner & Co KG, Köln 1981. 224 pp., bound, DM 24.80.—ISBN 3-7614-0517-0

Anionic Polymerization. Edited by *J. E. McGrath*. American Chemical Society, Washington 1981. 592 pp., bound, $ 45.95.—ISBN 0-8412-0643-0

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Anomalies of Liquid Water

By Elmar Wolfgang Lang and Hans-Dietrich Lüdemann*

Water at low temperatures ($T<300\,K$) reveals a multitude of unusual physico-chemical properties, which originate from the strong directivity of the hydrogen bonds. This directivity forces the molecules into a tetrahedral arrangement of first neighbors and thus leads to a poor packing efficiency. All anomalies of the liquid become more pronounced in the metastable range below the melting pressure curve. In the following article, methods for the investigation of the supercooled range are presented. A few anomalous static and dynamic properties are described and compared with the properties of normal liquids. The experimental results are discussed in the context of computer simulations and the more recent theories on cold water. It can be concluded that the anomalies of water, for instance the density maximum of the liquid phase and the initial decrease in viscosity with pressure, are confined to the pT-range: $T<300\,K$, $p\lesssim 200$ MPa. At these pressures, lowering the temperature leads to an unexpected behavior of almost all physical properties. They seem to approach a phase transition at $T\simeq(T_M-50\,K)$, the nature of which has not yet been fully characterized. This phenomenon has hitherto been observed only in supercooled water.— In the future it will be possible to use supercooled aqueous solutions for kinetic studies, thus expanding the available dynamic range for the investigation of aqueous solutions considerably.

1. Introduction

Water is the most abundant liquid on earth. Its high specific heat and the high energy of fusion of ice diminish the daily and seasonal variations of temperature at the surface of the earth and determine the climate. The unusual physical properties of water at temperatures around 300 K and atmospheric pressure, together with the unique chemical behavior of hydrocarbon compounds are the two prime essentials for a successful prebiological and biological evolution on the surface of the earth[1–4].

The pronounced tendency of the water molecule to participate with its two protons and two lone electron pairs in four hydrogen bonds simultaneously as donor and as acceptor, creates in the pure liquid a tetrahedral arrangement of first neighbors. This unusual open structure is the origin of all anomalies of liquid water and the ice polymorphs. The anomalies are also apparent in the high probability of the formation of irregular aqueous solutions of apolar compounds and in the occurrence of microheterogeneities in the distribution of dissolved non-electrolytes[5,6].

In aqueous solutions, proteins and nucleic acids can form ordered structures like helices or pleated sheets. For the generation of these structures, both intramolecular interactions as well as intermolecular interactions with the solvent water are of equal importance[7,8].

The contribution of the water molecules to the stability of these structures consists in the formation of intermolecular hydrogen bonds with the polar groups of the biopolymers and in the hydrophobic interaction, which forces

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apolar hydrocarbon groups into the interior of the polymers or leads *via* hydrophobic hydration to a change in water structure at the interface between apolar groups and solvent[9, 10].

The tendency to prefer a local arrangement of first neighbors with a tetrahedral geometry, resulting in a poor packing efficiency, increases with falling temperature and causes the density maximum in light water at 277 K and in deuterium oxide at 285 K. The unusual properties of water are much more pronounced at temperatures below the density maximum.

Unfortunately, the temperature of the density maximum is very close to the melting temperature. In the region of thermodynamic stability only a small range of temperatures is accessible to experiments. Thoroughly purified, clean water, which is free of all ice-nucleating impurities can be supercooled with avoidance of heterogeneous nucleation, and kept in the metastable state for long periods of time.

Supercooled water becomes easier to handle the smaller the metastable samples are, since the reduction in volume lowers the probability of the occurrence of heterogeneous nuclei. Therefore, most investigations of supercooled water have dealt with water contained in narrow capillaries[11], with small droplets of water in dust-free cloud chambers[12], or with droplets of water emulsified in a water-insoluble apolar carrier[13]. Such emulsions are stabilized by the addition of a water-insoluble emulsifying agent and can be kept in the supercooled, metastable state for periods of months. The emulsified aqueous phase can be supercooled to 233 K at atmospheric pressure[14]. The same homogeneous nucleation temperature T_H is found if water droplets are allowed to sink in a temperature gradient[12].

Water/cycloalkane-emulsions are suitable for the investigation of the pressure dependence of T_H. *Kanno, Speedy,* and *Angell*[15, 16] have studied T_H for H_2O and D_2O up to pressures of 300 MPa by differential thermal-analysis. The results of these studies (see Figure 1) show that T_H drops even faster with pressure than the melting temperature T_M and reveal that water can be supercooled to $-92\,^{\circ}C$ at 200 MPa. Increasing pressure thus enlarges the metastable range considerably.

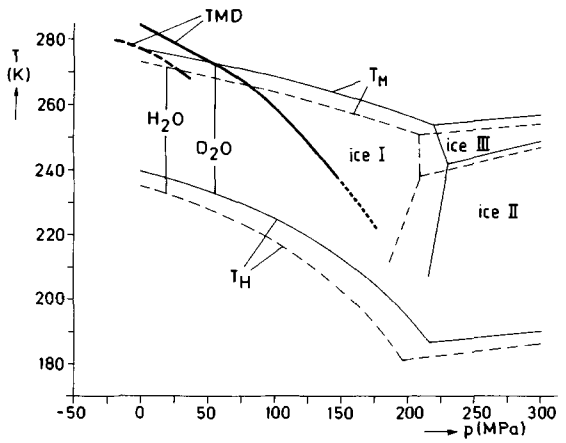


Fig. 1. *p-T*-projection of the phase diagram of H_2O and D_2O. T_M = melting temperature, T_H = homogeneous nucleation temperature [15, 16]. Also included is the temperature of maximum density (TMD) [87–90] (see Section 3.1).

In the following it will be shown using several examples, that the properties of metastable water are a continuation of the behavior observed in the range of thermodynamic stability, and that all anomalies of liquid water become considerably more pronounced in the supercooled region. A comprehensive review of the physical properties of supercooled water has been given by *C. A. Angell* in volume 7 of the series: "Water—A Comprehensive Treatise" edited by *F. Franks*[81].

2. The Equilibrium Structure of Liquid Water

2.1. Introductory Remarks

In principle one may calculate the macroscopic properties and the structure of a liquid from the physical properties of their molecules and the interactions between them. A rigorous quantum-mechanical treatment of a system with $\approx 10^{23}$ degrees of freedom is impossible and does not appear sensible since the microstates have energy differences of only $\Delta \approx \exp(-10^{23})$ erg and one can not decide by experiment which microstate the system acquires at any instant. Analogously it is impossible in classical mechanics to define the initial conditions for the equations of motion for a system of $\approx 10^{23}$ particles. In statistical mechanics macroscopic properties are expressed as averages weighted with proper distribution functions. The application of standard integral equations of statistical mechanics[17] to the description of liquid water has been attempted with relatively modest success[18–20]. In computer simulations[21] the averages are calculated numerically. Limited computer capacity and computer time permit these investigations on rather small systems with $\lesssim 10^3$ particles only. Two different methods of calculation are in current use: the molecular dynamics method (MD) solves the classical Newton-Euler equations of motion and forms time averages. The Monte-Carlo method (MC) forms ensemble averages. In systems of maximal 10^3 particles boundary effects play a major role; both methods thus apply either periodical boundary conditions and a cut-off radius for the interaction between the molecules or the Ewald summation[22, 23]. Besides these simulations, which will be discussed in the following, models describing liquid water as chemical equilibria between two or more possible states of the free or bound hydroxyl groups are presented in the literature and have been applied successfully[24, 25].

2.2. Model Potentials and Computer Simulations

The form of the intermolecular potential in the liquid phase is needed for MC- and MD-calculations. In simple liquids it is sufficient to consider pairwise interactions only. Quantum-mechanical calculations reveal however[26–28], that many-body interactions cannot be neglected in the case of liquid water. Since the exact form of the interaction potential in the liquid phase is unknown, computer simulations apply model potentials[29–32]. Such potentials are:

a) effective molecule pair potentials[33–35] which are constructed from point charge models and simple parame-

trized functions. The parameters in these functions are optimized to fit a few experimental properties (*e.g.* BNS[36-38], ST2[39-43], *Rowlinson*[44-46], TIPS methods[47]). These models do not take into account internal degrees of freedom and dissociation effects. If the electrostatic interaction between point charges is replaced by an electrical multipole expansion, one obtains non-additive potentials, which incorporate polarization effects[32].

b) parametrized functions (Coulomb potentials, exponential functions), which are fitted numerically to quantum-mechanical *ab initio* calculations of the dimer potential (*e.g.* MCY method[48-51,31,52,53]). These models do not take into account the influence of many-body forces.

c) empirical atom pair potentials between H- and O-atoms carrying the charge $\pm\eta e$ (*e.g.* CF methods[54-56]). These can also describe internal degrees of freedom and dissociation effects. The incorporation of non-additive interactions between delocalized charges, chosen in analogy to classical electrostatics leads to model potentials, which incorporate polarization effects[60-66].

The equilibrium structure of a molecular liquid is described by its atom pair correlation functions $g_{\alpha\beta}(R)$[29]. These can be determined by scattering experiments and calculated with computer simulations. Figure 2 gives

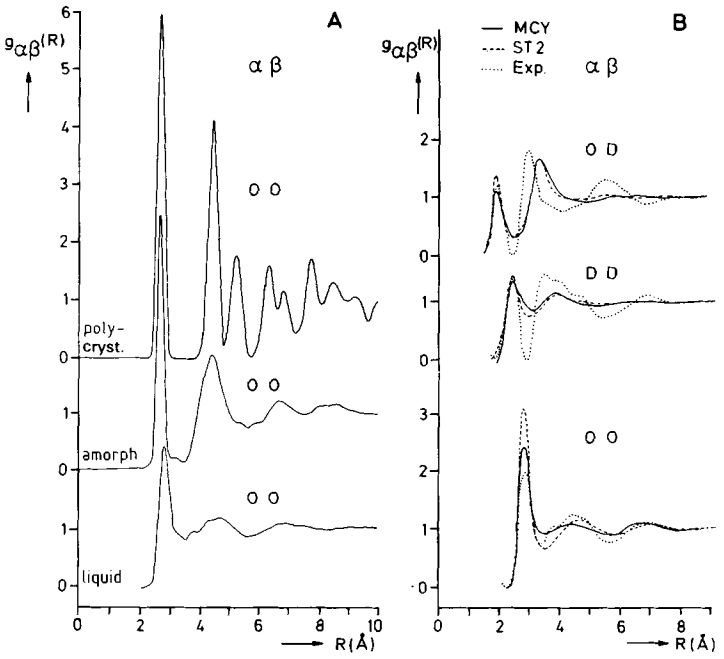


Fig. 2. Atom pair correlation functions $g_{\alpha\beta}(R)$ of liquid water. A) Comparison of the $g_{OO}(R)$ derived from X-ray studies for polycrystalline, amorphous, and liquid water (300 K) [74]; B) comparison between the calculated and the averaged experimental results $g_{\alpha\beta}(R)$ [182, 183] (MCY [48-51], ST2 [39-43] see text).

$g_{OO}(R)$ for H_2O in its various condensed phases. From the atom pair correlation functions one can derive that:

a) position and number of first neighbors is similar to the crystalline phases (tetrahedral coordination). The positions of the second neighbors show a broad distribution of O—O—O angles with the highest probability centered at the tetrahedral angle. Spatial correlations disappear for distances $R \gtrsim 8$ Å;

b) the maxima in $g_{OH}(R)$ and $g_{HH}(R)$ occur at distances expected for almost linear hydrogen bonds (for a detailed discussion see [29-32]).

At high hydrostatic pressures[43,67] $g_{OO}(R)$ becomes similar to the distribution functions of simple liquids.

The variations in the different $g_{\alpha\beta}(R)$ with increasing density reveal a bending of the hydrogen bonds and the formation of interpenetrating hydrogen bond networks. Taken together these results indicate that the equilibrium structure of liquid water is best described as a disordered network with more or less strained and bent hydrogen bonds. The topology of this network has been studied very thoroughly[39,53,68,69]. Classifying the molecules according to the number of hydrogen bonds formed, yields in all calculations a unimodal distribution. The distribution of polygons shows, that even and odd membered rings are found with comparable probabilities, the largest non-short-circuited rings containing 11 molecules. The analysis of the quasi-component distribution functions for hydrogen bond indices leads to a probability maximum for nonlinear H-bonds[53,69]. Furthermore, the degree of polymerization of a given configuration of water molecules and the structure and distribution of clusters with n water molecules has been investigated recently[70]. The statistical state of the H-bond network has been analyzed in terms of the average number of H-bonds per molecule ($\bar{n}$). At room temperature and at $\rho = 1\ g \cdot cm^{-3}$ the H-bond network exhibits for $\bar{n} \approx 1.3$ a bond-percolation threshold[*]. All estimates previously made for $\bar{n}$ under these conditions are significantly higher than this value, indicating that water is at any instant a space-filling network of H-bonded molecules. The time averaged mole fraction of loop-forming H-bonds is only greater than zero for $\bar{n} > 1.3$. This shows, that ring formation is a significant feature of the random H-bond network of liquid water[69].

The results discussed hitherto deal with the instantaneous structure (I-structure[71]) as obtained by the computer simulations. *Hirata et al.*[72] and *Belch et al.*[73] averaged the center of gravity- and angular-coordinates for a time of 0.2 ps, corresponding approximately to the period of hindered translations and librations, and created a structure comparable to the vibrationally averaged structure (V-structure) introduced by *Eisenberg* and *Kauzmann*[71]. This structure differs from the I-structure by:

a) a pair correlation function $g_{OO}(R)$ with a steeper and higher first maximum,

b) a stronger preference for almost linear hydrogen bonds,

c) a significant increase in the number of hydrogen bonds,

d) a strong increase in the number of non-short-circuited polygons of various size ($n = 3-11$).

[*] A bond percolation threshold is the first appearance of a H-bond network penetrating the whole sample.

These results are not very sensitive to the period of averaging. The stabilization of the disordered network in the V-structure is equivalent to the removal of mean thermal energy $k_B T$ from the I-structure. The hindered translations and librations can thus be understood as thermal excitations of the random H-bond network.

2.3. The "Random Network" Model[74]

The main result of the computer simulations is that liquid water presents a space-filling, random network of molecules interacting mainly through directional H-bonds of variable bonding energy and length. The network rearranges continuously on the time scale of diffusion processes, and for higher frequency vibrations it appears quasistatic. This picture has been combined with experimental data from the crystalline, the amorphous, and the liquid state to develop the "Random Network Model"[75,76].

In addition to the average distance between first neighbors R_{OO}, the quasistatic structure of the random H-bond network is described by the distribution of first neighbor distances ΔR_{OO}^2 and the deviation from a linear H-bond geometry θ_H^2 (θ_H = H-bond angle). Hindered translations and librations are treated as thermal excitations of this quasistatic network.

Sceats and *Rice*[77] completed their structural characterization of the disordered network in the RNM by the development of an interaction potential for the water molecules. Since this potential is derived from spectroscopic data it is obvious that it can only be valid for a rather limited range of the configuration space. However, it samples those configurations near the energy minimum, where the H-bond interactions strongly determine the mutual position of the molecules. The random network potential (RNP) is generated as a function of displacement from a standard reference configuration *via* a power series expansion. Only two coordinates are used, the first neighbor distance R_{OO} and the hydrogen bond angle θ_H.

The effective RNP is used together with the RNM for the calculation of thermodynamic potentials and static response functions[*]. The results are in good agreement with experimental data[73,78–80].

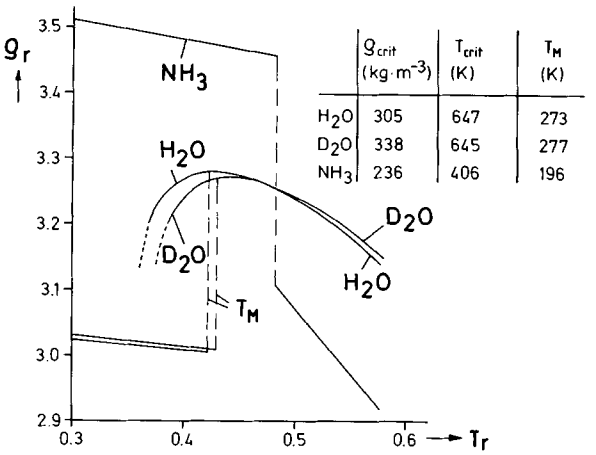
3. Static Properties of Supercooled Water

Only a few selected thermodynamic quantities are discussed in the following. It is shown, that the properties of the supercooled phase are a continuation of the behavior observed in the stable liquid phase. It is not attempted to approach encyclopedic completeness, but rather it is the intention to describe using a few examples the unique behavior of cold liquid water. A more comprehensive and extensive description of the state of the art is given by *Angell*[81]. His group has obtained many of the results described here.

[*] Static response functions are, *e.g.*, the thermal expansion coefficient α, the isothermal compressibility κ_T or the heat capacity at constant pressure C_p.

3.1. The Density ρ

The density at 0.1 MPa has been determined in thin capillaries of *ca.* 10 μm diameter for H_2O down to 239 K and for D_2O down to 244 K[82]. The resulting densities are in good agreement with data obtained in supercooled emulsions[14]. These data are given together with the results found in the region of thermodynamic stability[83] as reduced quantities ρ_r, T_r in Figure 3. In light water a density



	ϱ_{crit} (kg·m^{-3})	T_{crit} (K)	T_M (K)
H_2O	305	647	273
D_2O	338	645	277
NH_3	236	406	196

Fig. 3. ρ_r-T_r-diagram of H_2O and D_2O at 0.1 MPa and of NH_3 at saturation pressure. T_M: melting temperature.
$\rho_r \equiv \rho_{p,T}\rho_{crit}^{-1}$; $T_r \equiv TT_{crit}^{-1}$

maximum is observed at 277 K followed by a slight decrease of ρ on further lowering the temperature to the melting point. In the supercooled range this decrease in density is much more pronounced, and one would expect that $\rho_{liq}(T)$ becomes equal to the density of ice Ih[*] between 220—240 K. The expansion of volume starts much earlier in D_2O ($T_{\rho max} = 285$ K). At temperatures below ≈ 310 K, ρ_r of D_2O is lower than the reduced density of H_2O.

For a comparison Figure 3 gives the temperature dependence of ammonia[84,85], which as usual increases with falling temperature. Also the crystallization of this compound is accompanied by an increase in density.

Kanno and *Angell*[86] studied the pressure dependence of the density in supercooled D_2O to 243 K and 140 MPa. Figure 1 shows the pressure dependence of the temperature of maximum density (TMD) obtained from these measurements, together with previous studies on H_2O[87–89] which have been extended recently by *Henderson* and *Speedy*[90] to a negative pressure of −16 MPa. Extrapolation of the data obtained for D_2O implies, that the TMD becomes lower than T_H at pressures > 200 MPa. This anomaly of the supercooled liquid will thus not be observed at high pressures.

3.2. The Isothermal Compressibility κ_T

The isothermal compressibility of a substance is defined by

[*] Ice Ih is the hexagonal modification of ice thermodynamically stable at low pressures.

$$\kappa_T = -\left(\frac{1}{V}\right)\left(\frac{\partial V}{\partial p}\right)_T$$

In all simple liquids κ_T decreases rapidly with falling temperature.

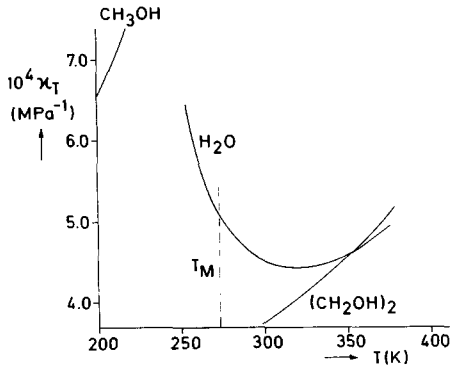


Fig. 4. Temperature dependence of the isothermal compressibility κ_T of H_2O at 0.1 MPa [91-93]. For comparison: κ_T of methanol [94] and glycol [95]. T_M: melting temperature.

In Figure 4 the compressibility of water at atmospheric pressure is given[91,92]. In the supercooled range the data were obtained by *Speedy* and *Angell* using a thin capillary. κ_T passes through a minimum at 320 K, a temperature well above the TMD (277 K), and increases below this minimum rapidly with falling temperature. On inspection of this diagram it becomes obvious, that the anomalies of the supercooled liquid are a steady continuation of the anomalies observed in the region of thermodynamic stability. For comparison, the compressibility of methanol[99] and glycol[95] are also included in the diagram. *Kanno* and *Angell*[86,96] succeeded in studying the compressibility of supercooled H_2O and D_2O at pressures up to 190 MPa down to a temperature of 243 K. They could show, that the increase in compressibility with falling temperature is still observed at the highest pressure studied, but it is less pronounced than at ambient pressure.

3.3. The Heat Capacity at Constant Pressure C_p

A supercooled liquid usually possesses a higher molar heat capacity than the corresponding crystalline phase. On further lowering the temperature more entropy is thus removed from the liquid than from the crystal.

The entropy of melting, which has remained in the supercooled liquid phase, is thus continuously removed on further cooling. From the third law of thermodynamics it must be inferred that the difference in molar heat capacity of the crystal and the metastable liquid is reduced with falling temperature. This is just what is observed in normal supercooled systems such as alcohols[97-99].

Figure 5 shows that C_p of ethanol and propanol decreases with falling temperature, and finally drops very rapidly, in a fairly narrow temperature interval in the range of the glass temperature T_g, to the value found for the crystalline phase.

Below a minimum temperature (T_{min} H_2O: 308 K, D_2O: 373 K) C_p^{Liq} of H_2O[100,101] and D_2O[102,103] increases with

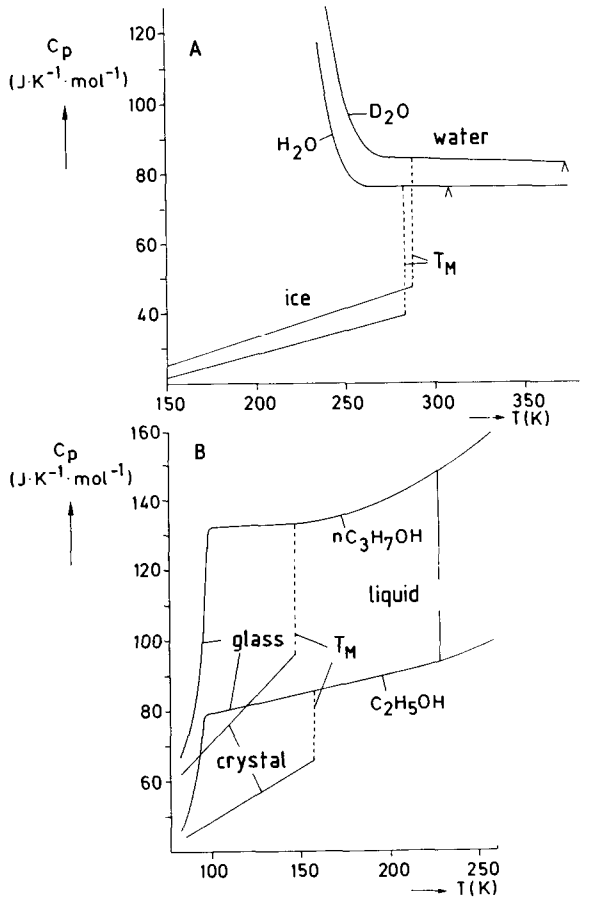


Fig. 5. Temperature dependence of the molar heat capacity at constant pressure C_p; A) of H_2O and D_2O [100-108], B) of 1-propanol and ethanol [97-99]. T_M: melting temperature.

falling temperature and this increase becomes very steep in the metastable region in the vicinity of the homogeneous nucleation temperature[104-108] (Fig. 1). Amorphous solid water, prepared by slow condensation of H_2O vapor under high vacuum conditions, has a glass temperature of $\approx 130-140$ K[109-110]. It is thermodynamically impossible that the decrease in C_p^{Liq} of supercooled water occurs in the vicinity of this glass temperature. The temperature dependence of C_p in the unstable interval of temperature is thus still a matter of controversy[107,108,111-113]. *Johari*[111] asserts that there is no continuity of states between the supercooled liquid phase and the amorphous solid phase prepared by low temperature condensation, while *Rice et al.*[113] propose the contrary. Recently, it has been claimed that a liquid emulsion was directly transferred into the glassy state by jet-cooling[114]. It is to be expected, that caloric studies on this phase will settle this controversy.

3.4. The Static Dielectric Constant ε_0

Figure 6 compares the temperature dependence of the static dielectric constant ε_0 of water in the range between 237 and 373 K[115,116] with the results obtained for methanol[117,118] and ammonia[119-122]. The data given for supercooled water were calculated from the dielectric constant of emulsions with low water content. Compared to the strong increase in ε_0 for methanol with falling temperature, supercooled water does not reveal any anomalies. The sug-

gestion[123] that supercooled water might approach a ferroelectric transition at temperatures around 220 K is thus rather improbable.

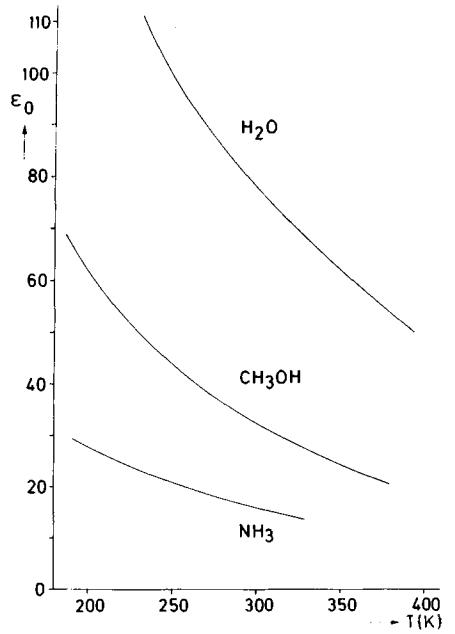


Fig. 6. Temperature dependence of the static dielectric constant ε_0 of H_2O [115, 116], methanol [117, 118], and ammonia [119–122] at 0.1 MPa.

The measurement of the static dielectric constant averages the dipole orientation in water over dimensions large compared to the particle diameter. The absence of a pronounced anomaly in ε_0 is thus an indication that the peculiarities of the structure of supercooled water are restricted to rather small domains, *i.e.* to the arrangement of the closest neighbors.

3.5. The Speed of Sound v

Several groups have studied the temperature dependence of the speed of ultrasound in liquid water into the supercooled region[112, 124–126]. *Trinh* and *Apfel*[127] could extend their measurements down to 240 K. The thermodynamic speed of sound v ($\nu \rightarrow 0$) is given by:

$$1/v^2 = \rho[\kappa_T - (TV\alpha_p^2/C_p)] \quad (1)$$

$$\left(\alpha_p = \frac{1}{V}\left(\frac{\partial V}{\partial T}\right)_p\right)$$

It thus follows from anomalies of ρ, κ_T, and C_p, discussed above that v should exhibit unusual properties, too. It is found that v decreases at $T \leq 347$ K with falling temperature[128], and apparently this decrease continues to the lowest temperatures studied[129] (Fig. 7). The results obtained by *Bacri et al.*[126] imply that the speed of sound continues to decrease rapidly with falling temperature and tends to zero, while the studies by *Trinh* and *Apfel*[127] indicate a minimum of the speed of sound at temperatures around 243 K. It must be emphasized, that the measurements in the supercooled region encounter considerable experimental difficulties, and it is not to be expected that they can have the precision of the investigations in the region of thermodynamic stability.

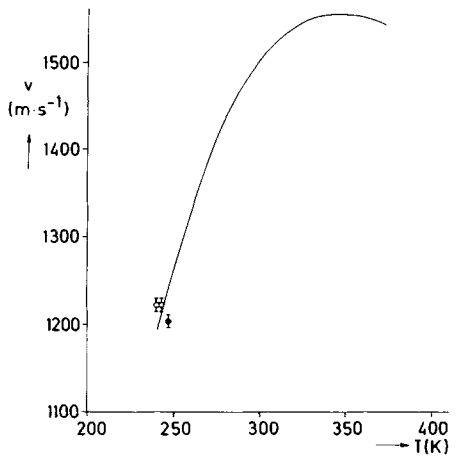


Fig. 7. Temperature dependence of the speed of sound v in supercooled water. Only the experimental points obtained at the lowest temperatures are given. • [126], ○ [127].

Recently *Dietz et al.*[194] estimated the heat conductivity λ in the supercooled range by application of a lattice model. Extrapolation of the experimental data for λ obtained at $T \geq 273$ K to lower temperatures by combining the experimental ρ, C_p, and v data yields the result that λ passes through a minimum at temperatures around 250 K and starts to increase on further cooling. Since this minimum is calculated for temperatures well above T_H, it would be interesting to verify this calculation by experiment, since then it could be decided which of the various models presented in the literature (see Section 4) quantitatively describes the properties of liquid water at temperatures approaching T_H and T_S (T_S is the singularity temperature, see Section 4.1 and Fig. 12).

4. Discussion of the Static Properties of Supercooled Water

4.1. The Speedy-Angell Singularity of Supercooled Water

The experimental findings given in Section 3 deal with the anomalies of water at constant pressure. These anomalies are almost completely suppressed if the properties of the liquid are studied at constant volume. The heat capacity at constant volume C_V, which can be calculated from the data given above by:

$$C_V = C_p - VT(\alpha^2/\kappa_T) \quad (2)$$

shows a quite normal behavior at atmospheric pressure.

Furthermore, it can be derived from the data that all anomalies of water are suppressed by high hydrostatic pressure ($p > 200$ MPa). It is thus the topology of the open, random three-dimensional H-bond network, which causes the anomalous behavior. This can be seen from the interrelations between the functions C_p, κ_T, α_p and the fluctuations of the thermodynamic variables in the (TPN)-ensemble[*]:

[*] A (TPN)-ensemble is a thermodynamic many particle system in which the temperature T, the pressure p, and the number of particles N are kept constant.

$\kappa_T \sim \langle(\delta\bar{V})^2\rangle$, $C_p \sim \langle(\delta S)^2\rangle$, and $\alpha_p \sim \langle\delta\bar{V}\delta S\rangle$.

It follows from the relations that the experimental pressure- and temperature-dependence of these quantities is determined by the density, enthalpy, and entropy fluctuations, which have strongly increasing amplitudes with falling temperature. From these observations *Speedy* and *Angell*[93] deduced the existence of a thermodynamic singularity in supercooled water at the temperature T_S. The latter is found only a few degrees below the homogeneous nucleation temperature T_H and, like T_H, is shifted with increasing hydrostatic pressure to lower temperatures (see Fig. 12). T_S is interpreted by the authors as a lower limit of mechanical stability of the supercooled liquid. This interpretation implies a divergence of the thermodynamic response functions in the vicinity of $T_S(p)$. The molecular origin of these anomalous fluctuations is seen in the formation of highly ordered clusters of the tetrahedral network with linear H-bonds.

Hydrostatic pressure opposes the formation of linear H-bonds, which correspond to the configuration with the lowest energy but with the largest volume requirements. Application of pressure thus leads to a decrease in the amplitudes of the anomalous fluctuations and to a rapid approach of the temperature of maximum density (TMD) towards the homogeneous nucleation temperature $T_H(p)$ (see Fig. 1). Currently (see als Section 10), two theoretical models exist for the description of the anomalous properties of supercooled water. The percolation model, proposed by *Stanley et al.*[130] (see Section 4.2), associates the conjectured thermodynamic singularity with a percolation threshold of the four-bonded water molecules in the random H-bond network. *Stillinger*'s[131] proposal, applying statistical mechanics of finite systems, shows that deep supercooling can eventually lead to a "thermodynamic catastrophe".

4.2. The Percolation Model

Stanley et al.[130, 132, 133], using the correlated site percolation theory, developed a concept for the qualitative description of the anomalies observed. This concept is, moreover, in quantitative agreement with computer simulations on model water. In this model, the water molecules are classified by the number of their hydrogen bonds. A fraction p_B of intact H-bonds is distributed randomly between the molecules. The fraction f_j of molecules of the species j is then given by the binomial distribution:

$$f_j = \binom{4}{j} p_B^4 (1-p_B)^{4-j} \tag{3}$$

Because $f_4 = p_B^4$, this model has a built-in amplification mechanism, which leads to a rapid nonlinear increase of four-bonded molecules with increasing p_B ($\triangleq$ falling temperature).

Although intact H-bonds are assumed to be distributed randomly between the molecules, a clustering tendency is observed especially for molecules of the species $j=4$. Obviously the local physical properties of the clusters of four-coordinated molecules, cannot be derived from the considerations given. They have to be introduced as plausible assumptions. Computer simulations show that clusters of tetracoordinated water molecules possess a density and entropy lower than the mean value of the liquid phase. This leads to density and entropy fluctuations larger than in a homogeneous network.

A direct experimental proof of the existence of these density fluctuations could be given by small-angle scattering experiments, since the structure factor $S(q)$ of a liquid is proportional to the Fourier transform of the density correlation function[134]. An increase in the correlation length ξ of the density fluctuations leads to an increase of $S(q)$ for $q \rightarrow 0$, and thus to a higher scattering intensity at small angles. *Bosio, Teixeira,* and *Stanley*[135] performed small-angle X-ray scattering experiments in supercooled H_2O and D_2O, which indeed showed this enhancement at small angles. At $T=253$ K the correlation length ξ of the density fluctuations amounts to approximately 8 Å.

4.3. The Differential Geometric Model[131]

This model starts with the partition function Z_N in the (TPN)-ensemble:

$$Z_N(\beta,p) = Z_N^{(0)} \langle \exp(-\beta\theta)\rangle_{TPN}; \quad \beta = kT^{-1} \tag{4}$$

where θ is the sum of the potential energy ϕ of the water molecules and the product pV. It is assumed, that the molecular configurations can be described by two independent parameters, the potential energy ϕ and the structural order parameter Ψ. The latter specifies the number of bound bicyclic octamers, which in a molecular dynamics calculation with the polarization model were found to represent a global minimum in the configurational space[63]. A system described by these parameters possesses essentially two stable states at low temperatures. The solid phase, characterized by a large Ψ and a small θ, and the liquid phase, for which θ becomes large while Ψ remains small.

Removal of thermal energy from such a system can lead eventually to a catastrophe, *i.e.* to a divergence of the order parameter Ψ for the liquid phase. Just this situation may arise in supercooled water at the temperature T_S. Since Ψ is a measure of the number of bound bicyclic octamers, which represent open structures with linear H-bonds in the irregular H-bond network, the fluctuations of the order parameter are consequently associated with density fluctuations of the H-bond network. Diverging density fluctuations imply a divergence of the functions κ_T, α_p, and C_p.

An important implication of both the differential geometric model and the percolation model is, that the aggregation of ordered regions, or analogously the percolation of four-coordinated clusters of molecules, creates an irreversible situation, leading to the destruction of the liquid phase, *i.e.* to homogeneous nucleation. It will thus be fairly difficult to follow experimentally the temperature dependence of physical properties to the immediate vicinity of T_S.

A significant difference between the two model-considerations given above should be emphasized once more: While the proposals by *Speedy* and *Angell*[93] and by *Stillinger*[131] (Section 4.1) lead to a divergence of the static prop-

erties (κ_T, C_p, α_p) on approaching T_S, the ideas developed by *Stanley* and *Teixeira*[132] lead to the conclusion, that these properties should show in their percolation model no divergence when the percolation threshold T_S is approached.

As explained by *Bosio, Teixeira,* and *Stanley*[135] scattering experiments at very small scattering angles at temperatures above T_H could decide whether the correlation length (ξ) of the density fluctuations diverges at T_S or runs through a maximum above T_H.

5. Dynamic Properties of Liquid Water

In statistical mechanics the dynamic properties of liquids are described by time correlation functions of dynamic variables[136]. The theoretical calculation of these functions for molecular liquids is exceedingly complicated. Many time correlation functions have, however, been calculated explicitly in computer simulations of model water.

5.1. Molecular Dynamic Calculations

Only the molecular dynamics method can yield dynamic properties. Contrary to the investigations of the structural aspects of liquid water the dynamic properties of this liquid have been studied by computer simulation in a few cases only.

In statistical mechanics, translational motions in a liquid are described by velocity autocorrelation functions $\varphi(t)=\langle\vec{v}(0)\vec{v}(t)\rangle$. The velocity correlation function for the center of gravity of the molecule $\varphi_{CM}(t)$ has been determined over a wide range of temperatures for "BNS-water"[37,38] and "ST2-water"[40,41]. At low temperatures this function shows pronounced oscillations around $\varphi_{CM}(t)$ for short times ($t<0.5$ ps). The spectral density function reveals significant maxima at ≈ 40—$60\ cm^{-1}$ and 190—225 cm^{-1} at low temperatures. These are shifted with rising temperature to lower frequencies. These bands have been identified as the O—O—O bending and the O—O stretching vibrations, respectively. Though these oscillations—compared to simple liquids—are very pronounced, they are still strongly damped, and $\varphi(t)$ decreases to zero after approximately 1 ps. As emphasized by *Rahman* and *Stillinger,* these oscillations do not imply diffusional jumps from one discrete equilibrium position to another. The translational motions of the water molecules rather occur as a continuous process within the perpetual rearrangement of the labile, disordered H-bond network. The self diffusion coefficient D is a quantitative measure characterizing the diffusive motion of the center of gravity of the molecules in a homogeneous liquid. By application of a Green-Kubo relation it can be described with the correlation function $\varphi(t)$:

$$D = (1/3)\int_0^\infty \langle\vec{v}(0)\cdot\vec{v}(\tau)\rangle\,d\tau \qquad (5)$$

The temperature dependence of D is significantly weaker for BNS-water and ST2-water than found experimentally. Incorporation of long range interactions *via* a reaction field leads to a calculated diffusion coefficient twice as large as the experimental result[137]. Molecular dynamic calculations with CF-potentials[55] yield at room temperature diffusion coefficients which are a factor of 2 to 3 too low. *Rapaport* and *Scheraga*[50] performed molecular dynamic calculations with the MCY-potential. The diffusion-coefficients obtained are for slightly supercooled water $\approx 67\%$ too large, and at 377 K $\approx 12\%$ too small. As in the case of BNS-water and ST2-water they also show a temperature dependence weaker than that observed by experiment. Thus it can be concluded, that all model potentials are unable to describe correctly the strong decrease of D in the supercooled range. The only determination of D from molecular dynamic calculations of ST2-water under high pressure[43] yields at 370 K for an increase in density by 35% a lowering of D by $\approx 10\%$. Experimentally a reduction by this amount is already seen for a change of density by $\approx 6\%$, indicating that ST2-water reveals much smaller pressure effects than real water. It is still an open question, whether molecular dynamic calculations will show the increase of D with pressure which is observed experimentally at low temperatures and medium pressures (<250 MPa).

In addition to the translational motions the molecules in a liquid possess rotational mobility. These rotations are described in statistical mechanics by the functions

$$G_l(t)=\langle P_l[\vec{u}_j(0)\cdot\vec{u}_j(t)]\rangle$$

which describe the time dependence of the orientational correlation of a unit vector $\vec{u}$ in the molecule j. The functions for l = 1, 2 are closely related to measurable quantities[138]. *Rahman* and *Stillinger*[37,38] studied the orientational relaxation of water molecules in molecular dynamic calculations applying the BNS-potential. $G_1(t)$ as well as $G_2(t)$ reveal librational motions for $t<0.1$ ps. For longer time spans both functions decay nearly exponentially. The effective time constants τ_1 and τ_2 of the exponential decay decrease with falling temperature. *Van Gunsteren et al.*[137] determined τ_1 and τ_2 for ST2-water with a reaction field, while *Rapaport et al.*[50] calculated τ_1 by application of the MCY-potential. Both latter groups obtain significantly smaller time constants than found for ST2-water, which yields the best agreement with experiment. With the exception of the data for supercooled water, the temperature dependence of τ_1 and τ_2 is in good agreement with experimental results.

The librational behavior of the molecules has been further investigated by *Rahman* and *Stillinger*[37,38] by studying the angular velocity autocorrelation function

$$f_\alpha(t)=\langle\omega_\alpha(0)\omega_\alpha(t)\rangle;\quad \alpha=x, y, z$$

A weak time dependence of $f_\alpha(t)$ implies a relatively free rotation, while fast oscillations of this function indicate that the molecule is kept in a fixed orientation by its neighbors. All three functions show strong oscillations, which, however, decay very rapidly ($<10^{-13}$ s at 307 K). The first neighbor molecules are thus unable to retain a "cage molecule" in its orientation for times $t>10^{-13}$ s. Increasing

temperature weakens the oscillations, the periods of oscillation becoming longer under these conditions.

5.2. Statistical Mechanics and Hydrodynamics

In 1978 *Chu* and *Sposito*[139] studied the motion of the center of gravity of the water molecules with a time-dependent perturbation theory by application of classical statistical mechanics. The authors start with the so-called "relaxing-cage" model[140] for the dynamic structure of an atomic liquid and generalize it for the case of liquid water. Ice Ih is chosen as the undisturbed reference system, yielding the normal modes for the lattice dynamics of the system. The calculation of the velocity autocorrelation function

$$\varphi(t)=\langle\vec{v}(0),\vec{v}(t)\rangle$$

starts at a time $t=0$ with a liquid possessing a first neighbor order corresponding to ice. This first neighbor arrangement is assumed to have the same normal modes as ice Ih. The destruction of this arrangement through the thermal motion of the neighboring molecules causes the decay of the normal modes. Collisions with neighboring particles leads to a continuous loss of correlation for the velocity of the particles. After a short period of time the cage structure is almost intact, and the central molecule oscillates. The thermal motion of the neighbors destroys the first neighbor arrangement and the oscillating motion of the central particle is transformed into a diffusive motion. By suitable choice of the lifetimes of the normal modes, the spectral density function of this model can satisfactorily reproduce the power spectrum derived from molecular dynamic calculations.

Sposito[141] shows in a subsequent paper, with data from the literature for the self-diffusion coefficient D, the dielectric relaxation time, τ_d and the NMR-orientational correlation time τ_2, that at low temperatures and pressures the single particle motion in liquid water can be adequately described with a hydrodynamic model. In the hydrodynamic approximation one obtains with $f=\beta a/3\eta$:

$$D=\frac{k_B T}{4\pi\eta a}(1+f)/(1+3/2f) \tag{6}$$

$$\tau_d \simeq \tau_1=\frac{4\pi\eta a^3}{k_B T}f/(1+f) \tag{7}$$

$$\tau_2=\frac{4\pi\eta a^3}{3k_B T}f/(1+f) \tag{8}$$

where η is the shear viscosity, a the van der Waals radius of the water molecule, which is assumed to be spherical, and the parameter β characterizes the boundary conditions at the surface of the sphere[142]. The equations imply $\tau_1/\tau_2=3$, and thus the validity of the rotational diffusion model[143]. Using experimental viscosity data and $a=1.44$ Å one can reproduce the experimental results for D, τ_1, and τ_2 very well, under the assumption that for translational diffusion $\beta\simeq 0$ and for rotational diffusion $\beta\rightarrow\infty$.

6. Transport and Relaxation Properties of Supercooled Water

6.1. The Shear Viscosity η

The viscosity η describes the transport of linear momentum in a liquid. Kinetic processes as well as intermolecular forces contribute to this transport. Theory shows, that the viscosity summarizes the influence of short-lived processes, decaying on the time scale of the mean collision time τ_c[144], upon the dynamics of the system at long times.

Experimental investigations of the temperature- and pressure-dependence of the shear viscosity have been performed with high accuracy in the region of thermodynamic stability of the liquid[145-147]. The strong temperature dependence of the viscosity in cold water is amplified further in the metastable supercooled phase. At ambient pressure, η could be measured down to 238 K for H_2O and to 242 K for D_2O[148,149] (Fig. 8).

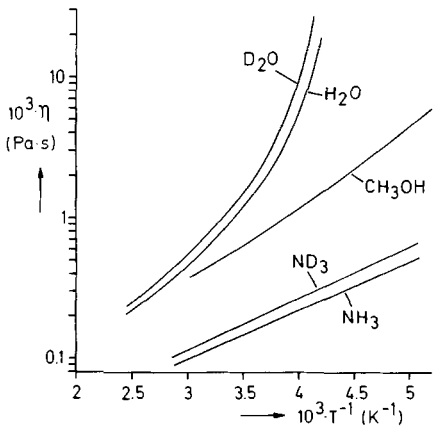


Fig. 8. Temperature dependence of the shear viscosity η of H_2O, D_2O [145-149], methanol [188], NH_3, and ND_3 [184-187].

The pressure dependence of the viscosity reveals anomalous behavior in cold water (H_2O: $T\leq 312$ K, D_2O: $T\leq 317$ K[150]), since in water—contrary to simple liquids—η decreases with increasing pressure and passes through a minimum. The minimum pressure increases with falling temperature, and the minimum becomes narrower[151,152]. Measurements at elevated pressures $p>0.1$ MPa have not been published for the metastable phase. An interpolation between the experimental results obtained down to 258 K at high pressures and the results at ambient pressure indicates a drastic drop in the viscosity with increasing pressure. The ratio $[(\eta(D_2O))/(\eta(H_2O))]_{T,p}$ increases rapidly with falling temperature.

6.2. The Self Diffusion Coefficient D

The self diffusion coefficient D describes the motion of the center of gravity for the particles in a liquid. In the thermodynamically stable region of the liquid phase, nu-

merous measurements of the temperature- and pressure-dependence of D are published for H_2O as well as for D_2O[145, 146]. For the metastable supercooled phase only the temperature-dependence of the diffusion coefficient at normal pressure is known to 242 K[153] (see Fig. 9).

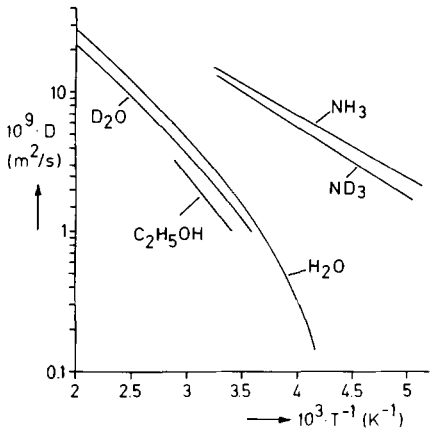


Fig. 9. Temperature dependence of the self diffusion coefficient D of H_2O, D_2O [145, 146, 153–156], ethanol [192], NH_3 and ND_3 [184–191] at saturation pressure.

The viscosity η as well as D do show a pronounced temperature dependence[154], which is even more pronounced in the supercooled liquid[155]. In cold water D passes with increasing pressure through a maximum[154–156], which, with falling temperature, is shifted to higher pressures[152].

6.3. The Spin Lattice Relaxation Rate R_1

Determination of the nuclear magnetic spin-lattice-relaxation rate R_1 offers a possibility of collecting information about molecular motions in liquid water. Application of a semiclassical theory yields[157]:

$$R_1 = \frac{1}{T_1} \approx \sum_{m=1,2} c(m) J^{(m)}(m\omega_0) \qquad (9)$$

where T_1 is the spin lattice relaxation time determined experimentally, $J(\omega_0)$ the spectral density of the autocorrelation function $G(t)$ at the observing frequency ω_0. The factors $c(m)$ characterize the type and strength of the interaction between spin system and lattice. The time dependence of the fluctuation function $G(t)$ can often be described by a microscopic correlation time τ, characterizing the molecular motion.

Spin lattice relaxation times T_1 have been measured in water for the isotopes ^1H, ^2H, and ^{17}O over a wide range of pressures and temperatures[158–166]. Until now the proton- and deuteron-T_1 are the only physical quantities that could be studied in the whole metastable region of the liquid phase down to temperatures $T \geq T_H$ (see Fig. 10) and up to pressures of 300 MPa[164, 165].

In non- or weakly-associated liquids[167] T_1 can normally be described by a simple Arrhenius equation. For water a non-linear temperature denpendence is seen in the Arrhenius diagram, the deviations being most pronounced in the supercooled region. Hydrostatic pressure leads to a smaller

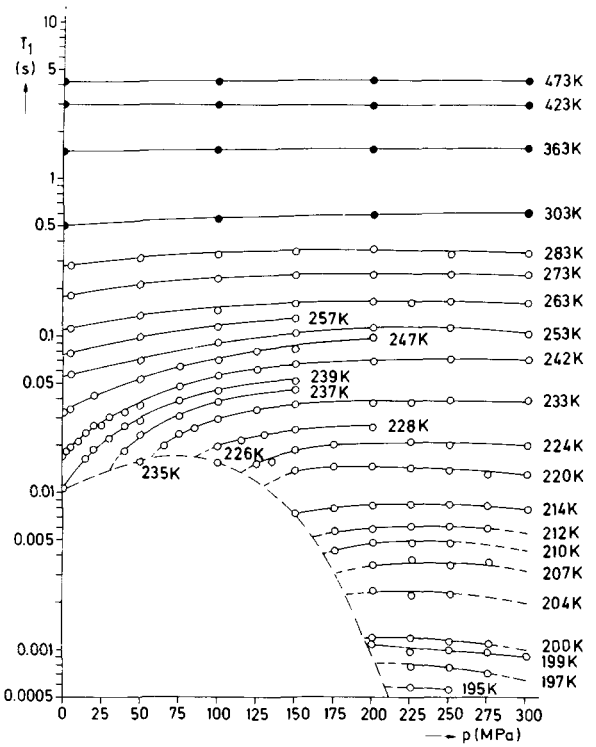


Fig. 10. Pressure dependence of the isotherms of the deuteron spin-lattice relaxation time T_1 in D_2O. • [151, 152], ○ [165].

isobaric temperature-dependence of T_1[165]. The isothermal pressure-dependence of T_1 in cold water reveals—as found for the pressure coefficients for η and D—an extremum[168]. With falling temperatures this anomaly becomes,

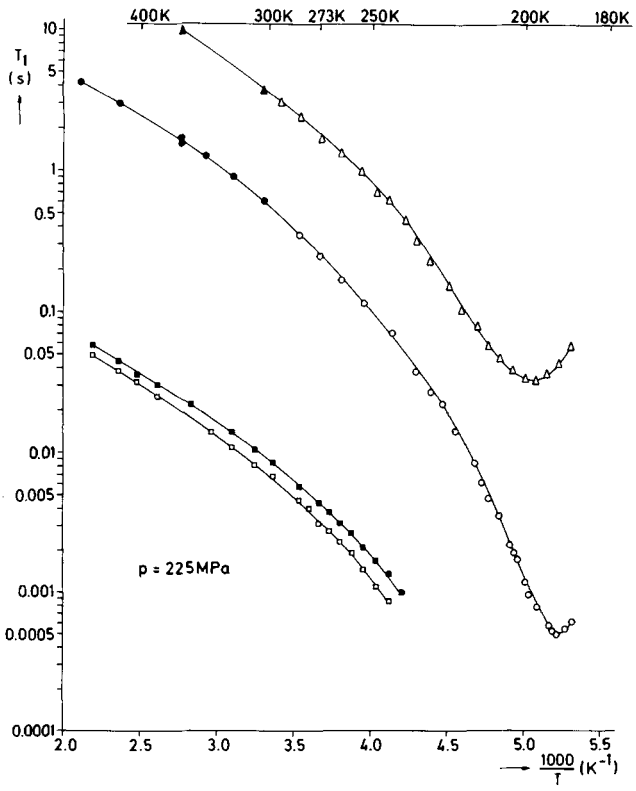


Fig. 11. Temperature dependence of the 225-PMa isobars of the spin-lattice relaxation time T_1. ▲ [193], △ [164] (^1H-T_1 in H_2O); ● [193], ○ [165] (^2H-T_1 in D_2O); ■ [166] (^{17}O-T_1 in H_2O); □ [166] (^{17}O-T_1 in D_2O).

compared to the range of thermodynamic stability, much more pronounced in the supercooled region at medium pressures ($p < 200$ MPa)[164-167]. At very low temperatures ($T < 220$ K), because of the pressure dependence of the homogeneous nucleation temperature T_H this means necessarily higher pressures, T_1 decreases monotonously with pressure, as observed in simple liquids[167, 169-171].

A minimum in the high-pressure T_1-isobars for the proton- and deuteron-relaxation was observed close to the homogeneous nucleation temperature T_H (see Fig. 11). Such minima occur if the microscopic time constant becomes approximately equal to the observing frequency ($\omega_0 \tau \simeq 1$), since at high temperatures $R_1 \approx \tau$ and at low temperatures $R_1 \approx (\omega_0^2 \tau)^{-1}$, and since τ increases monotonously with falling temperature. Measurements of the relaxation time T_1 at various frequencies in this temperature region could provide the possibility of determining details of the form of the spectral density function $J(m\omega_0)$. An interpretation of microscopic correlation times τ, derived from the T_1-measurements, will be given in Section 7.

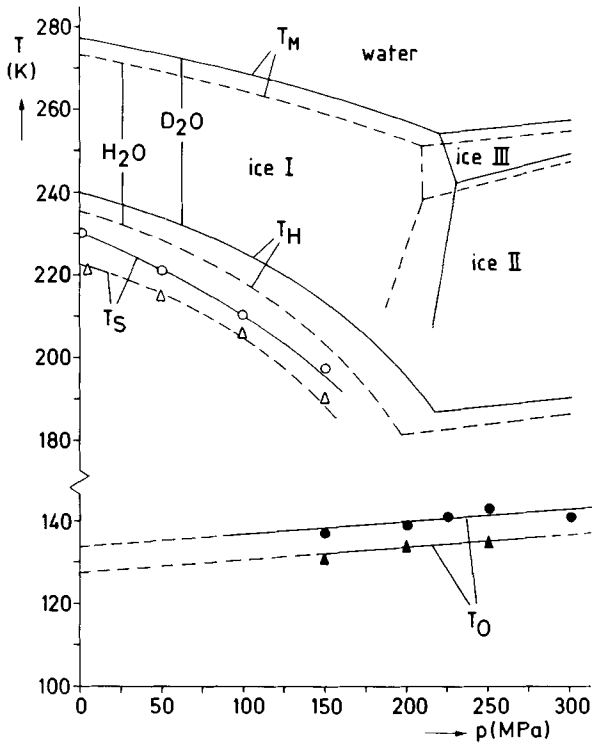


Fig. 12. p-T-Projection of the phase diagram of H_2O and D_2O, including: T_S = temperature of singularity, T_0 = ideal glass transition temperature. △, ▲: H_2O; ○, ●: D_2O. T_S was obtained by fitting the τ_2 data to the Speedy-Angell equation.

7. Discussion of the Dynamic Properties of Supercooled Water

The discussion of the static and dynamic properties of liquid water shows that water at elevated pressures reveals the behavior of a normal viscous liquid[172]. The isobaric temperature-dependence of the dynamic properties of many viscous liquids is described quantitatively by the Vogel-Tammann-Fulcher equation[173-175].

$$X = X_0 \exp\left(\frac{B}{T - T_0}\right) \quad \text{(VTF equation)} \tag{10}$$

This equation indicates that the dynamic quantity X diverges on approaching the temperature T_0. In viscous liquids this occurs if the liquid is transformed into the amorphous glassy state, in which molecular mobility is frozen out. The temperature T_0 is called the ideal glass transition temperature. It has been shown[165, 166], that at high hydrostatic pressures ($p \geq 200$ MPa) the isobaric temperature dependence of the orientational correlation time τ_2 of liquid water can be described quantitatively by the VTF equation. The parameters t_0, B, T_0 obtained from least squares fitting of the experimental τ_2 to the VTF equation are compiled in Table 1. The ideal glass temperatures $T_0(p)$ found show a small positive linear pressure-dependence (Fig. 12). These data, as well as their extrapolation to normal pressure are in good agreement with published T_0-data[176]. Comparison of the results obtained in light and in heavy water reveals a significant isotope effect. In D_2O, T_0 is higher by about ≈ 6 K than in H_2O, in accordance with the lower zero point energy of heavy water. The two other parameters of the VTF-equation also reveal an isotope effect. It appears interesting to compare the dependence of the pre-exponential factors τ_0 on the isotopic composition. The reciprocal values τ_0^{-1} have the dimension of a frequency and correspond in the energy spectrum of liquid water to the librations of the molecules, originating from the hydrogen bonding interaction with its neighbors. This interaction confines a molecule for a short period in its orientation and forces it to oscillate about the equilibrium position. In accordance with the isotope-dependence of the librational bands, one finds a ratio

$$\frac{\tau_0^{-1}(D_2O)}{\tau_0^{-1}(H_2O)} \simeq \sqrt{\frac{I(D_2O)}{I(H_2O)}} = 1.38 \tag{11}$$

equal to the square root of the mean moments of inertia I of the molecules. *Sceats et al.*[75] interpreted the librational

Table 1. Parameters of the VTF-equation (10), obtained from the least squares fitting of τ_2 to this equation (σ = standard deviation).

p [MPa]	$T_0 \pm 2$ [K]		$B \pm \sigma$ [K]		$(\tau_0 \pm \sigma) \times 10^{-14}$ [s]		Corr.-coeff.	
	D_2O	H_2O	D_2O	H_2O	D_2O	H_2O	D_2O	H_2O
150	137	131	633 ± 3	652 ± 5	6.6 ± 0.3	4.6 ± 0.3	0.9998	0.9996
200	139	134	604 ± 3	623 ± 7	6.1 ± 0.5	4.6 ± 0.5	0.9997	0.9992
250	143	135	563 ± 3	581 ± 5	7.0 ± 0.6	5.9 ± 0.3	0.9997	0.9986

motions as thermal excitations in the quasistatic hydrogen bond network. Therefore, τ_0^{-1} characterizes the high-frequency orientational fluctuations of the molecules in the potential wells. The exponential factor summarizes the influence of the topological reorientation of the disordered H-bond network caused by the thermal fluctuations.

Removal of thermal energy decreases the probability for configurational fluctuations and thus leads to an increase in the orientational correlation times τ_2. It is to be expected, that at high pressure these fluctuations also determine the temperature dependence of the self-diffusion coefficient and the shear viscosity, and that these are described also by the VTF-equation. But the experimental data on deeply supercooled water at high pressures required in order to test this suggestion are still lacking.

For lower pressures ($p < 150$ MPa), it could be shown[165, 166] that the orientational correlation time τ_2 decreases with falling temperature much faster than predicted by the VTF-equation. As the discussion of the static properties showed, their temperature dependence is determined by a thermodynamic singularity at the temperature T_S. It has to be checked whether this description is also applicable to the dynamic properties of cold liquid water. The isobaric temperature-dependence of the orientational correlation time τ_2 at low pressures ($p \leq 150$ MPa) is quantitatively described by equation (12) proposed by *Speedy* and *Angell*[93]:

$$X = A_X \left(\frac{T - T_S}{T_S}\right)^{-\gamma_X} \quad \text{(Speedy-Angell equation)} \qquad (12)$$

which is known from the theory of critical phenomena. The parameters obtained from a least squares fit of the experimental data to equation (12) are given in Table 2. From the data it becomes apparent that the change from H_2O to D_2O influences the singularity temperature T_S only. Fig. 13 shows, that the τ_2 for both liquids fall in a reduced diagram ($\ln \tau_2 \leftrightarrow \ln(T - T_S)$) upon a single straight line. The dynamic behavior of the water molecules in both liquids is thus identical at equal distance from the singularity temperature ($T - T_S$). The frequencies τ_S^{-1} derived from the factors τ_S ($\equiv A_X$) correspond in the spectrum of liquid water to the O—O—O bending vibrations. The ratio of these hindered translational vibrations on isotopic H-D-substitution is given by the ratio of the square root of the molecular masses ($= 1.05$). It is thus understandable that no isotope effect outside the limits of error is found for τ_S.

The results suggest, that fluctuations in the H-bond bending vibrations are the driving force for the anomalous density fluctuations. The growth and decay of these vibrations controls the orientational correlation function $G(t)$ at low temperatures and pressures.

From the definition of the orientational correlation time by

$$\tau_2 = J(\omega = 0) = \int_0^\infty G(t)\,dt \qquad (13)$$

it follows, that the orientational fluctuations are determined by low frequency excitations of the random network.

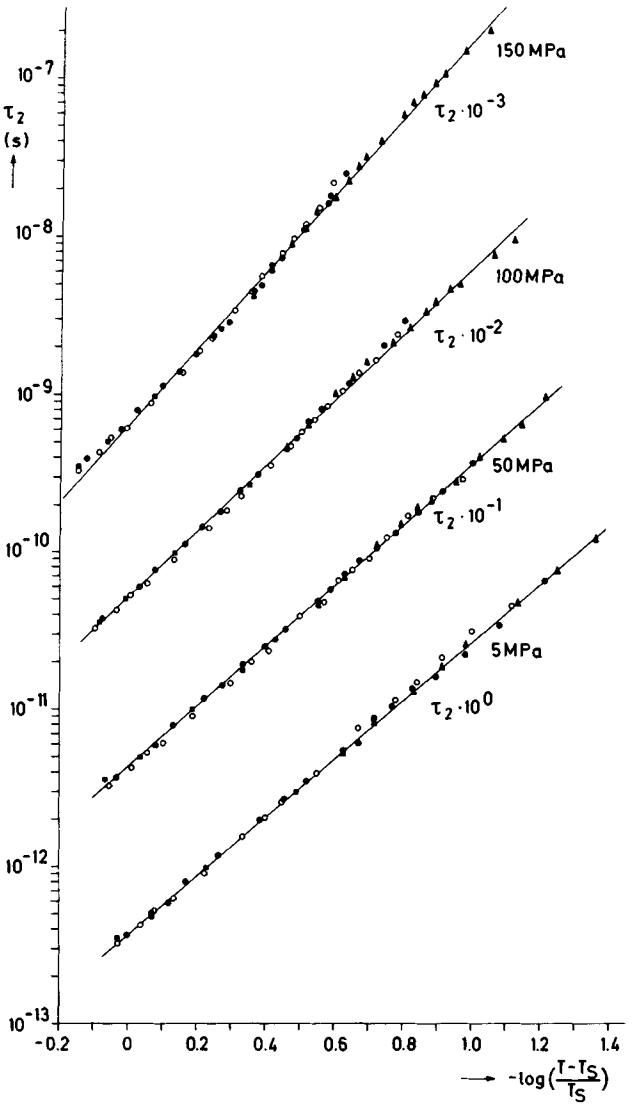


Fig. 13. Representation of some τ_2-isobars as function of the reduced temperatures [166] (τ_2: orientational correlation time, T_S singularity temperature). ○ Calculated from $^{17}_{8}$O-T_1 in $H_2{}^{17}O$; ● calculated from $^{17}_{8}$O-T_1 in $D_2{}^{17}O$; ▲ calculated from $^{2}_{1}$H-T_1 in D_2O [165]; ■ calculated from $^{2}_{1}$H-T_1 in D_2O [151, 152].

Table 2. Parameters of the Speedy-Angell-equation (12), obtained from the last squares fitting of τ_2 to this equation (σ = standard deviation).

p [MPa]	$T_S \pm 2$ [K]		$\gamma \pm \sigma$		$(\tau_S \pm \sigma) \times 10^{-13}$ [s]		Corr.-coeff.	
	D_2O	H_2O	D_2O	H_2O	D_2O	H_2O	D_2O	H_2O
0.1	230	223	1.85 ± 0.01	1.89 ± 0.05	3.74 ± 0.1	3.42 ± 0.1	0.9998	0.9991
5	229	221	1.87 ± 0.02	1.87 ± 0.02	3.67 ± 0.2	3.67 ± 0.2	0.9993	0.9993
50	221	215	1.93 ± 0.02	1.96 ± 0.02	4.23 ± 0.1	3.78 ± 0.1	0.9996	0.9997
100	210	204	2.11 ± 0.02	2.11 ± 0.02	4.95 ± 0.1	4.95 ± 0.1	0.9994	0.9992
150	196	189	2.37 ± 0.1	2.56 ± 0.1	6.73 ± 0.2	6.00 ± 0.2	0.9991	0.9978

H-bond bending vibrations can develop the better, the more open and ordered the random H-bond network is. They are thus dependent upon the presence of ordered patches with almost linear H-bonds. The discussion of the static properties suggested that the cooperative order-disorder fluctuations of the random H-bond network reflect the formation of such open-structured, low density clusters on approaching T_S. These processes also hinder the reorientation of the molecules, and cause the orientational correlation time τ_2 to increase drastically in the vicinity of T_S.

It is interesting to check whether the temperature dependence of D or η also is described by equation (12). At ambient pressure the dynamic properties D (self-diffusion coefficient), η (shear viscosity) and τ_2 (orientation correlation time) of liquid water can be quantitatively represented by the Stokes-Einstein equation (14) and the Debye equation (15):

$$D = kT/4\pi\eta a \tag{14}$$

$$\tau_2 = 4\pi a^3\eta/3kT \tag{15}$$

The result of this test is that the correlations $\tau_2 \sim \eta/T \sim 1/D$ are also valid for the supercooled phase. After introduction of the corresponding temperatures $(T - T_S)$, all dynamic properties of H_2O and D_2O fall onto a single straight line. Within the limits of error all lines have identical slopes $\gamma = -1.9 \pm 0.1$, the plausible explanation being that the development of ordered patches in the random H-bond network slows down the reorientation and self diffusion of the molecules and increases the shear strength of the H-bond network.

8. Supercooled Aqueous Salt Solutions

The influence of solutes upon the structure and dynamics of water must become more pronounced in the supercooled region. Figure 14 collects some deuterium-T_1 measurements on supercooled salt solutions[176]. The specific influence of the ions upon T_1 is much more pronounced at 238 K than at 283 K. In this context it appears interesting that at low temperature and low pressure, all ions increase the mobility of the water molecules. Under these conditions magnesium and lithium ions cause the breaking of water-structure.

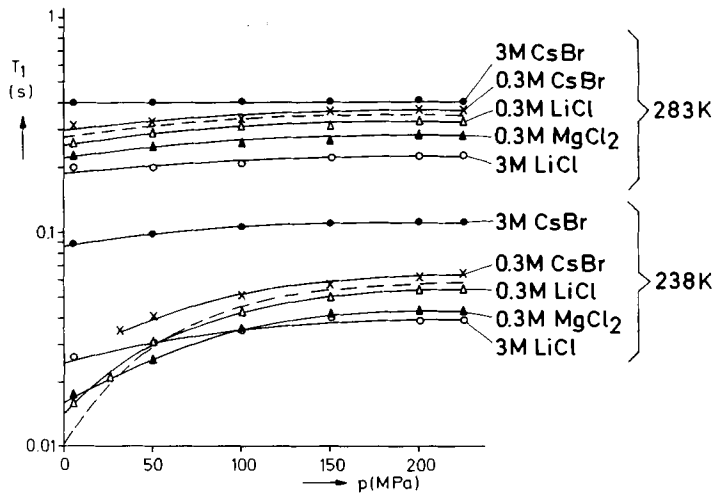


Fig. 14. Pressure dependence of the isotherms of the deuterium spin-lattice relaxation time T_1 of some salt solutions in D_2O.

9. Concluding Remarks

In the preceding chapters it has been shown that liquid water has to be regarded as a three-dimensional random H-bond network. Locally, an almost tetrahedral arrangement of nearest neighbors is preferred in this network. A broad distribution of O—O—O angles leads to a loss of spatial correlation between more distant molecules. The network possesses thermal excitations in the form of hindered translations and librations. The structural rearrangements occur on the time scale of diffusion processes. Removal of thermal energy stabilizes linear H-bonds and favors a network topology with open structure and low density. Especially in supercooled water, these patches have a tendency to clump together.

The consequence of these cooperative processes is that many thermodynamic and dynamic properties possess a very strong temperature dependence in the metastable region. It cannot be decided, as yet, whether a second-order phase transition, or a percolation threshold, or a stability limit is approached with falling temperature. Hydrostatic pressure destabilizes the hydrogen bonds and leads to a denser packing of the molecules in the network. The formation of ordered low density patches becomes more difficult, and is thus suppressed by increasing pressure. Under high hydrostatic pressure the properties of water reveal a pressure- and temperature-dependence similar to many simple viscous liquids. So far only a few measurements of the physical properties of deeply supercooled water at high pressure are available. Considerable experimental difficulties are encountered in the metastable range, particularly if the experiments cannot be performed on the relatively stable alkane/water emulsions.

No computer simulations for deeply supercooled water have been performed hitherto, since the considerable increase in the microscopic time constants on approaching T_H, the temperature of homogeneous nucleation, increases the computer time required enormously. Calculations in the metastable region would, on the other hand, show whether the potential functions applied are able to reproduce the cooperative behavior of the molecules. The anomalies, which are much more pronounced in the supercooled water, present an important test case for all simulations.

It is to be expected that experiments with supercooled aqueous solutions of biopolymers, apolar solutes, and electrolytes will contribute substantially to our understanding of these solutions in their respective regions of thermodynamic stability[177-181]. The investigation of the dynamic properties of water in supercooled aqueous solutions of biopolymers should yield new insights into the hydration of these substances, since large deviations from the behavior of pure water are to be expected. The investigation of the kinetic activity and of the spectroscopic properties of enzymes under these conditions extends the observ-

able dynamic range of enzymic reactions by some orders of magnitude[195]. Unstable reaction intermediates could be accumulated and investigated spectroscopically[180, 181]. During the winter season many cold-blooded, polar animals produce antifreeze agents, most of which are glycoproteins[196–199]. The formation of these compounds enables the animals to survive for long time spans at a few degrees below the melting point of their body fluid. The physics of this freeze-protection mechanism is not completely understood and it should be possible to check some of the currently discussed mechanisms with the help of spin-lattice relaxation time measurements of the water molecules in deeply supercooled solutions of these compounds.

Furthermore, one can expect that the investigation of supercooled aqueous emulsions with apolar solutes will increase our knowledge about hydrophobic solvation and hydrophobic interactions.

10. Appendix

After submission of this review article for publication, *Wu, Whalley,* and *Dolling* published high-pressure data up to 1560 MPa for neutron scattering in D_2O[200]. It emerges that the number of nearest neighbors increases about 50% between 0.1 MPa and the highest pressure achieved. The first O—O distance, on the other hand, remains practically unchanged. In addition, further work published by *Angell, Sichina,* and *Oguni*[201] revises C_p values for supercooled H_2O and D_2O. However, the basic conclusions of Section 3.3 are not affected by this revision. Finally, *Speedy*[202] has succeeded in describing the behavior of supercooled and superheated liquid water assuming a closed mechanical stability limit for the liquid.

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Transition Metal Complexes with *cyclo*-Triphosphorus (η^3-P_3) and *tetrahedro*-Tetraphosphorus (η^1-P_4) Ligands

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Salts of 3d, 4d, and 5d metals in the presence of the ligands 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos) or tris(2-diphenylphosphinoethyl)amine (np_3) react with white phosphorus P_4 (or yellow As_4) to produce several mononuclear sandwich and dinuclear triple-decker sandwich complexes, which contain the unprecedented *cyclo*-triphosphorus (or *cyclo*-triarsenic) unit acting as a *trihapto*-ligand. In these complexes the metal atoms are bonded to the three phosphorus atoms of the phosphane ligand and to the three atoms of the *cyclo*-P_3 or *cyclo*-As_3 unit. The complexes are diamagnetic or have μ_{eff}-values corresponding to one or two unpaired electrons. The *cyclo*-P_3 ligand is coordinatively unsaturated as proved by the fact that the mononuclear sandwich compounds may form Lewis-base adducts with electron-acceptor fragments. Reaction of the complexes $(np)_3M$ (M = Ni, Pd) with white P_4 leads to formation of diamagnetic compounds $[(np_3)M(\eta^1\text{-}P_4)]$, in which the metal atom is bonded to the three phosphorus atoms of the np_3-ligand and in addition to one P atom of the intact P_4 molecule, which behaves as a *monohapto*-ligand. This article contains a review of the syntheses and structures of these complexes as well as a unified, albeit qualitative, approach to their bonding and properties.

1. Introduction

Very few metal complexes containing P_2, P_3, or P_4 groups bonded to the metal atom were known until recently. Some rather unstable compounds of the types $[RhCl(ER_3)_2(P_4)]_2$ (E = P, As; where E represents an element with donor properties)[1], $[Fe(CO)_4]_3P_4$, and $[Fe(CO)_3P_2]_n$[2] had been reported, but definitive conclusions about their structures were not reached. Unstable tetrahedral clusters $P_n[Co(CO)_3]_{4-n}$ (n = 1, 2, 3) had been reported and structures proposed for some of them on the basis of indirect evidence[3].

Recently however, stable compounds containing the *cyclo*-triphosphorus (P_3) unit or, only in two cases, the *tetrahedro*-tetraphosphorus (P_4) molecule as ligands have been obtained by allowing some hydrated salts or complexes of transition metals to react with white phosphorus in presence of appropriate polyphosphanes under mild conditions. X-ray structure determinations performed on some of these compounds have shown that the tetrahedral P_4 molecule in the complexes hitherto obtained behaves as a *monohapto*-(η^1) ligand and is coordinated to *one* metal atom, whereas the *cyclo*-triphosphorus group acts as a *trihapto*-(η^3) ligand and is either (a) coordinated to *one* metal atom or (b) to *two* metal atoms, or (c) is η^3-bonded to *one* metal atom and *in addition* is η^1-bonded to one to three other metal centers.

The *cyclo*-triphosphorus complexes of type (a) have the general formula $[LM(\eta^3\text{-}P_3)]^{n+}$, where L = 1,1,1-tris(diphenylphosphinomethyl)ethane, $(CH_3C(CH_2PPh_2)_3$, triphos) or tris(2-diphenylphosphinoethyl)amine, $(N(CH_2CH_2PPh_2)_3$, np_3), M = metal and n = 0, 1[4-7]. They may be considered as "sandwich" compounds in a generalized sense, since their LM moieties are isolobal[9, 10] with the η^5-C_5H_5M fragment which is present in some of the classical sandwich compounds[8]. The dinuclear metal complexes of type (b) are formed by the triple-decker sandwich complexes $[LM(\eta^3\text{-}P_3)M'L]^{n+}$[4, 11], in which the *cyclo*-triphosphorus unit forms the "filling" between the molecular fragments ML and M'L. Several complexes of this type are paramagnetic and have provided, with the analogous *cyclo*-triarsenic derivatives, the first examples of paramagnetic triple-decker sandwich complexes[4, 12]. The polynuclear complexes of type (c) have less simple structures than those of types (a) and (b) (see Section 5).

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2. Metal Complexes with *tetrahedro*-Tetraphosphorus Ligands

2.1. Synthesis and Structure

Reaction of the trigonal pyramidal nickel(0) complex $(np_3)Ni$[13] with white phosphorus in tetrahydrofuran (THF) at *ca.* 0 °C leads to the diamagnetic compound $[(np_3)Ni(\eta^1\text{-}P_4)]$, which readily precipitates[14]. This is slightly air-sensitive and is insoluble in all common organic solvents. On substitution of $(np_3)Pd$ for $(np_3)Ni$, the $[(np_3)Pd(\eta^1\text{-}P_4)]$ complex is obtained by the above procedure[15]. This is isomorphous with the nickel analog, whose structure has been determined[14].

The metal atom in $[(np_3)Ni(\eta^1\text{-}P_4)]$ is bound to the three P atoms of the np_3 ligand and to one P atom of the P_4 unit in a nearly regular tetrahedral coordination geometry (Fig. 1). The molecule has crystallographic C_3 symmetry, with the threefold axis passing through the metal atom, the coordinated P_4 phosphorus atom, and the nitrogen atom of the np_3-ligand, which is uncoordinated. In the educt compound this nitrogen donor is linked to the metal: its detachment upon coordination by one phosphorus atom of the competing P_4 ligand results from the flexibility of the

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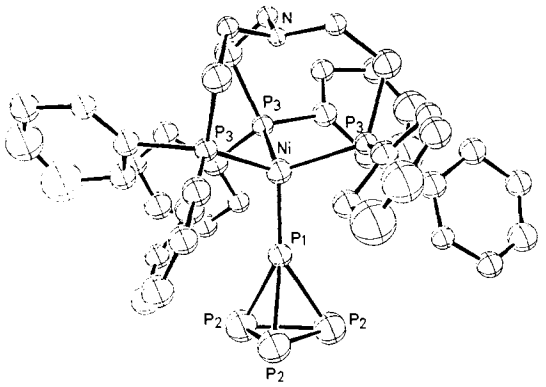

Fig. 1. Perspective view of [(np$_3$)Ni(η^1-P$_4$)] in the crystal.

np$_3$ molecule[16, 17], and is probably determined by the electronic factors described in Section 2.2. Upon coordination, the P_4 unit undergoes a small distortion from regular tetrahedral geometry with PP bond distances of 2.21 Å[18], to form a slightly elongated trigonal pyramid, with the apex pointing toward the metal atom: the P_{basal}—P_{apical} distances of 2.20(3) Å are significantly longer than the P_{basal}—P_{basal} of 2.09(3) Å, even though there is a rather large uncertainty on such values due to the limited diffraction data available for structure determination. Such deformations of the tetrahedral P_4 unit and the short Ni—P bond (1.99(1) Å) are indicative of considerable interaction between the (np$_3$)Ni moiety and the P_4 group, although it has to be stressed that the energy required to change the length of PP bonds is rather small.

The formation and stability of these P_4 adducts are probably due to properties of the np^3-ligand, such as its flexibility, the nature of its donor atoms, and its ability to impose a proper symmetry on the metal environment, as well as to the stability of the 18-electron configuration of the metal atom, existing both in the educt and in the product. In fact, at variance with most of the reactions leading to formation of η^3-P$_3$ complexes described in Section 3, the formation of the present P_4 adducts involves no change in the oxidation number of the metal atom. It appears that a moderate conformational rearrangement of the ligand molecule is sufficient to lengthen, *via* the simplest reaction path, the NiN bond with formation of the new NiP bond by the incoming P_4 molecule. This transformation leads to an almost regular tetrahedral environment of nickel(0), formed by four phosphorus atoms, which should be more favorable than the less symmetrical and inhomogeneous arrangement of the parent compound.

2.2. MO Description of the Bonding

A qualitative description of the electronic structure of the *tetrahedro*-P_4 derivatives is provided by the "fragment molecular orbital" (FMO) approximation[19, 20]. The nature of the valence orbitals of a conical fragment such as the (np$_3$)M moiety with uncoordinated nitrogen atom has been extensively investigated and described at length[9, 21]: this will be described briefly here, since it is relevant to most of the following discussion. The HOMO (Fig. 2a) consists of a doubly-degenerate 3e orbital set (the electron count is appropriate for the d^{10} configuration, although assigning electronic configurations to molecular fragments is to some extent arbitrary) having high metal nd and low (n+1)p character. Due to the low "pyramidality"[9] (PMP ≈ 109°) of the (np$_3$)Ni fragment, the orbitals forming the "lower d block", *i.e.* the 1a$_1$ (z^2, σ-type) and the 2e set, are located only slightly below this. As a further consequence of the large PMP angle, mixing of the (xz,yz) and (xy,x^2-y^2) sets of metal orbitals occurs in the 2e and 3e MO's which therefore have less pronounced δ- and π-bonding character, respectively, than in more pyramidal (*e.g.* in the (triphos)M) fragments. Lower-lying orbitals have predominantly ligand character. The LUMO, 2a$_1$, is an important σ-bonding hybrid orbital with metal (n+1)s and (n+1)p character.

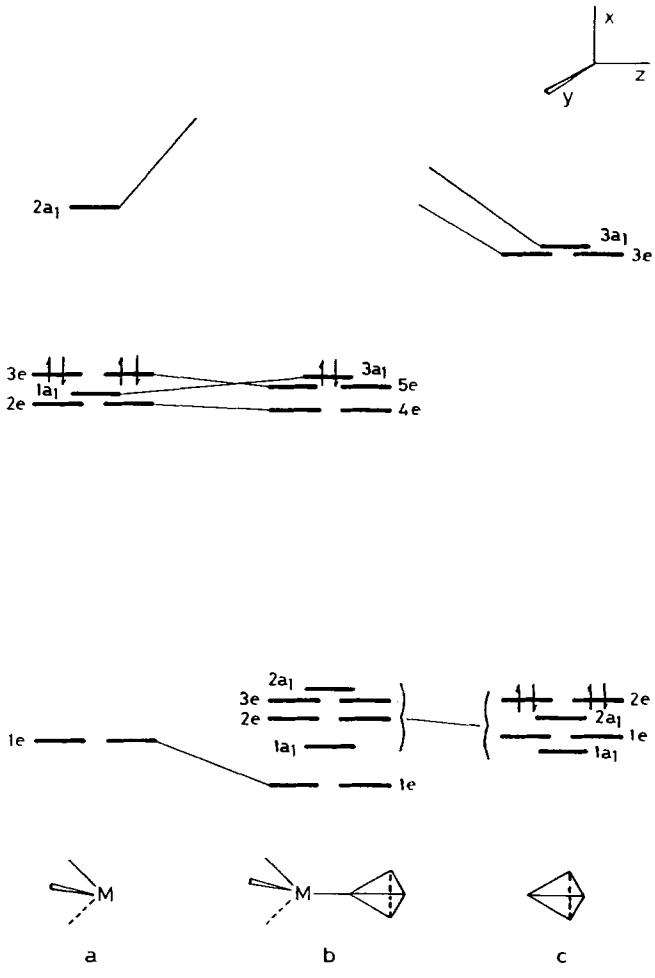

Fig. 2. MO correlation diagram for [LM(η-P$_4$)] complexes (C$_{3v}$ symmetry); a, b, c see text.

This MO correlation diagram (Fig. 2), as are those in Figures 5 and 10, is based on extended-Hückel (EH) calculations[22] performed using computer programs, which we wrote following procedures described by *Hoffmann et al.*[9, 10, 19–22] with parameters from this or other sources[23]. Both iterative calculations, to self-consistency in charge and configuration (SCCC), and noniterative ones, in which the effects of geometrical deformations were investigated, were performed. In the simplified molecular models, the triphosphane in the (np$_3$)M or similar LM fragments was idealized as a set of three properly oriented PH_3 groups.

The energies of the important orbitals of the P_4 group, which in the calculations was assigned the distorted geometry in $[(np_3)Ni(\eta\text{-}P_4)]$, are shown on the right-hand side of the interaction diagram (Fig. 2c). Even when the effects of the small decrease from T_d symmetry are taken in account, their order does not match the energy sequence reported by *Van Wazer et al.* based on accurate calculations on the isolated P_4 molecule[24]; the corresponding energies, on the other hand, all lie rather close together.

None of the interactions between valence orbitals on the two fragments appear to be particularly strong (Fig. 2b), in contrast to what would be anticipated from consideration of the bond lengths (Section 2.1). Important stabilizing effects in these adducts are due to the sp hybrid orbital on the metal atom, as well as to additional vacant orbitals on both fragments. There are indications that the empty d orbitals on the phosphorus atoms play a role in redistributing the electron density throughout the whole molecule. However such effects can hardly be quantified, because of the lack of reliable parameters for virtual orbitals.

The largest contribution to the bonding in the P_4 adducts is provided by the σ-type $2a_1$ orbital (Fig. 2b) having metal z^2, z contributions, and above all apical-phosphorus s and z contributions. The bonding and antibonding π-interactions between the two fragments largely cancel each other out, and hence contribute slightly to the overall $MP(P_4)$ overlap population (which is, however, appreciably larger than that of the $MP(np_3)$ bonds). Allowing the apical nitrogen atom, treated as an NH_3 group, to approach the metal atom more closely results in an increase in the $NNiP(np_3)$ angle and causes a steep rise in the energy of a σ orbital, which is antibonding with respect to the $MP(P_4)$ bond. This reillustrates the validity of the 18-electron rule.

The increasing difficulty in obtaining $[(np_3)M(\eta^1\text{-}P_4)]$ compounds on going from nickel to palladium, and then to platinum (the platinum derivative has not been obtained as yet using the previously mentioned procedure) is presumably due to increasing mismatch of the orbital energies of the two fragments involved.

The electronic spectra of these d^{10} complexes show a band at 26000–27000 cm^{-1}, which may be due to a $M \rightarrow L$ charge-transfer (CT) transition. The absence of lower-energy excitations suggests that bands appearing at much lower energies in the spectra of the η^3-P_3 derivatives (see Section 3.4) may have some d-d character.

3. Mononuclear Metal Complexes with *cyclo*-Triphosphorus Ligands

3.1. Synthesis

If hydrated cobalt(II) complex salts with "non-coordinating" anions such as BF_4^- are allowed to react under mild conditions with white phosphorus in presence of triphosphanes, mononuclear single- or dinuclear triple-decker sandwich complexes are obtained, depending on the stoichiometric ratio of the reagents. Both types of complexes contain the *cyclo*-P_3 group as ligand. This group, originating from the P_4 molecule, behaves as a *trihapto*-ligand both when it is coordinated to *one* metal atom and when bridging between two metal atoms. The mononuclear sandwich complexes are obtained using an excess of white phosphorus dissolved in THF[5,7]; the hydrated metal salts employed in the reactions are generally dissolved in ethanol whereas the triphosphane is in THF solution. The complexes are stable in air but only moderately stable in organic solvents.

The structure of $[(triphos)Co(\eta^3\text{-}P_3)]$[7], which is typical of complexes of this sort, is shown in Figure 3. The metal

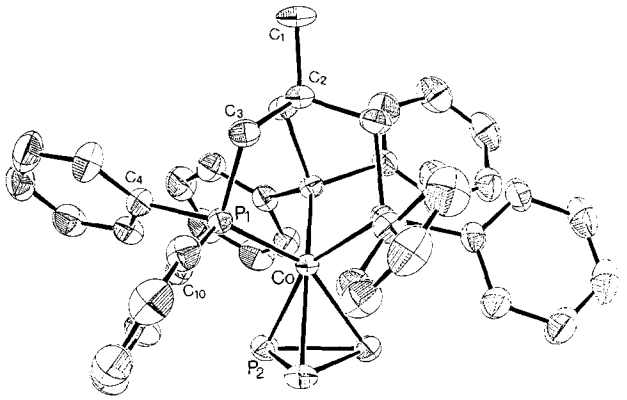

Fig. 3. Perspective view of $[(triphos)Co(\eta^3\text{-}P_3)]$ in the crystal.

atom is coordinated by six phosphorus atoms, three of which are provided by the triphos ligand, the other three by the *cyclo*-P_3 group. Viewed along the molecular C_3 axis the two sets of donor atoms are nearly staggered, yielding a very distorted octahedral coordination. A closely similar molecular geometry exists in $[(np_3)Co(\eta^3\text{-}P_3)\cdot 0.5\,C_4H_8O]$ (Fig. 4), in which the np_3 nitrogen atom is not coordinated[5]. Simple electron counting (Section 3.2), shows that removal of the nitrogen lone pair from the coordination sphere of the metal allows this to attain the 18-electron configuration.

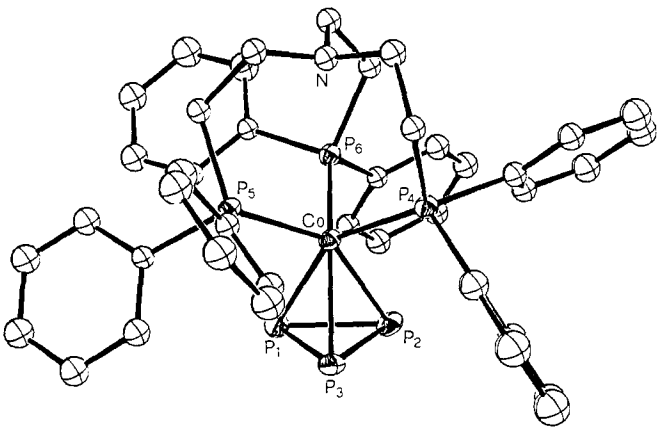

Fig. 4. Perspective view of $[(np_3)Co(\eta^3\text{-}P_3)]$ in the crystal.

The rhodium and iridium analogs of $[(triphos)Co(\eta^3\text{-}P_3)]$ have been obtained by allowing the complexes $[Rh(C_2H_4)_2Cl]_2$ and $[Ir(PPh_3)_2(CO)Cl]$, respectively, to react with P_4 in presence of triphos[6]. These complexes are isomorphous with each other as well as with the cobalt complex[6].

Starting from the $[(MCl_2PBu_3)]_2$ complexes (M = Pd, Pt), the first cationic sandwich complexes of *cyclo*-P_3, $[(triphos)M(\eta^3\text{-}P_3)]^+$ (M = Pd, Pt), have been obtained[15]. The structures of their BF_4^- salts, which are mutually isomor-

phous, have been determined[15,25]. Although the coordination geometry is closely similar to that of the Co, Rh, and Ir neutral complexes, the MP and PP distances show significant differences between the two sets of compounds. Selected structural data for all of the mononuclear complexes are listed in Table 1. The main features of the structures are shortly discussed in Section 3.3 using a simplified approach to the bonding.

At variance with the η^1-P_4 complexes, in the mononuclear η^3-P_3 compounds substantial interaction occurs between the upper d-block orbitals, 2e, of the LM fragment and properly oriented orbitals, e″, of the η^3-P_3 fragment. Stabilizing effects of the sp hybrid orbital on the metal atom and of additional virtual orbitals are again important. The appreciable contribution to the bonding by the metal (n + 1)s and (n + 1)p orbitals increases on going from

Table 1. Structural data for the mononuclear [LM(η^3-P_3)] complexes [a, b].

Compound	Distances			Angles		Ref.
	MP(L)	MP(P_3)	PP	PMP [c]	PMP [d]	
[(triphos)Co(η^3-P_3)]	2.186(1)	2.301(1)	2.141(2)	93.55(4)	55.43(5)	[7]
[(np_3)Co(η^3-P_3)]	2.254(9)	2.315(8)	2.135(6)	102.7(6)	54.9(2)	[5]
[(triphos)Rh(η^3-P_3)]	2.294(1)	2.418(2)	2.152(2)	91.25(4)	52.86(5)	[6]
[(triphos)Ir(η^3-P_3)]	2.277(2)	2.436(2)	2.159(4)	91.22(7)	52.60(8)	[6]
[(triphos)Pd(η^3-P_3)]BF_4	2.37(1)	2.412(8)	2.115(8)	91(2)	52.0(1)	[15]
[(triphos)Pt(η^3-P_3)]BF_4	2.339(8)	2.433(5)	2.155(9)	91(1)	52.6(3)	[25]

[a] L = triphos or np_3. [b] The average bond-lengths (chemically equivalent bonds) [Å] and -angles [°] are reported; standard deviations are calculated using the formula $[\Sigma_i|\Delta_i|^2/(n-1)]^{1/2}$, where n is the number of bonds or angles and Δ_i are deviations of individual values from the mean. [c] Angle involving P atoms of L. [d] Angle involving the P atoms of *cyclo*-P_3.

It should be noted that formation of mononuclear *cyclo*-P_3 derivatives by the procedures exploited up to now, invariably involves reduction of the metal atom relative to its oxidation state in the parent compound. The mechanisms of the reactions have not yet been ascertained. We recall at this point that a *cyclo*-P_3 cobalt derivative with formula $[(CO)_3CoP_3]$ had been obtained previously by different procedures using more drastic conditions[3].

3.2. MO Approach to the Bonding

Among the possible simplified approaches to the bonding in the mononuclear *cyclo*-P_3 derivatives the following two seem to be particularly appropriate. According to the first viewpoint the compounds may be considered to originate from the tetrahedral P_4 molecule by replacing one of the phosphorus atoms with an LM (M = Co, Rh, Ir; L = triphos, np_3) or an LM^+ (M = Pd, Pt) group. Such substituent groups are three-electron donors according to *Wade*'s rules[26]: in this sense they are equivalent to the phosphorus atom of P_4 that they are considered to replace. This is essentially the approach followed by *Dahl et al.* in their pioneering work on metal carbonyls containing the As_3 or As_2 group as ligands[27,28]. In a more detailed approach the bonding pattern is investigated by the FMO approximation (see Section 2.2).

The orbital correlation diagram for an [LM(η^3-P_3)] complex is shown in Figure 5. The orbitals of the LM conical fragment (Fig. 5a) have already been described (Section 2.2, Fig. 2); the triphosphane lone pairs, lying lower in energy, do not appear in the diagram. Orbitals of the *cyclo*-P_3 group having suitable energy to interact with those of the other fragment are shown on the right hand side (Fig. 5c): those labeled a_1' and e′ lie in the plane of the ring, whereas a_2'' and e″ represent π orbitals of the fragment, *i.e.* normal to its plane. The energy levels of the complex are sketched in Figure 5b.

complexes with 3d and 5d metals. The large separation between the HOMO and LUMO is in good qualitative agreement with the diamagnetism of the compounds and with their electronic spectra, which exhibit transitions only at high energies (see Section 3.4).

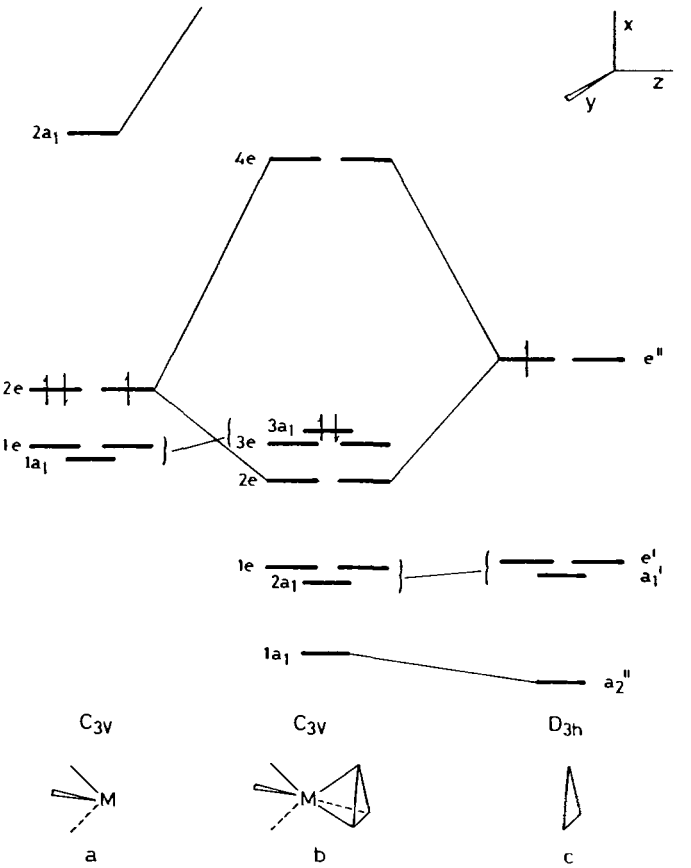

Fig. 5. MO correlation diagram for $[LM(\eta^3\text{-}P_3)]^{n+}$ complexes; a, b, c see Text.

It is a useful approximation for electron-counting purposes to consider the η^3-P_3 group as a three-electron donor both in the mononuclear and in the dinuclear complexes. This assumption is based on the fact that among the highest-occupied orbitals of the *cyclo*-P_3 group, those (a_2'' and e'' in Fig. 5c) which undergo most of the interaction with orbitals of the other fragment(s), are allocated three electrons. From a complementary point of view, such assumption is consistent with the assignment of the stable 18-electron configuration to all the mononuclear *cyclo*-P_3 derivatives, nine electrons being provided by the metal atom or ion, six by the triphosphane lone pairs and the remaining three by the neutral *cyclo*-P_3 group[*].

Iterative SCCC calculations indicate that there is an overall shift of electron density toward the *cyclo*-P_3 group in η^3-P_3 complexes. Although the amount of this shift may not be reliable, as it may be largely an artifact of the calculational procedure, the trend however should be correct (it is supported by comparisons with $[(CO)_3M(\eta^3\text{-}P_3)]$ and $[Cl_3M(\eta^3\text{-}P_3)]$ model systems). The general shortening of the PP distances in these compounds (Table 1) from the value of 2.21 Å found for the isolated P_4 molecule[18], can, therefore, hardly be attributed to decreased electrostatic repulsions between lone pairs on the phosphorus atoms. It may originate from an overall increase in bonding and/or decrease in antibonding interactions within the ring upon coordination to the metal atom. Remarkably, the $MP(P_3)$ overlap integral is two to three times smaller than that of "normal" MP bonds, such as those formed by the phosphane (L) donor atoms. The PP overlap population is almost twice as large as that of an MP(L) bond.

3.3. Structural Trends

Turning to a consideration of structural features of the mononuclear compounds, the fact that the $MP(P_3)$ bonds are generally longer than the MP(L) bonds (cf. Table 1) may be traced to the above differences in the overlap integrals. A further point is that the close similarity in the PP and $CoP(P_3)$ distances in the two cobalt compounds $[(triphos)Co(\eta^3\text{-}P_3)]$ and $[(np_3)Co(\eta^3\text{-}P_3)]$ (cf. Table 1) is surprising in view of the differences both in their CoP(L) bond lengths (0.07 Å) and in the PCoP angles (9°) formed by the phosphane donor atoms. The difference in the angles, *i.e.* in the "pyramidality" of the LM fragments, in particular, would be expected to have appreciable stereochemical consequences[10,29]. It appears that the conformational preferences of the two LM fragments are inhibited by the strict bonding requirements of the "rigid" *cyclo*-P_3 ring. Calculations on two model systems, which correspond to each of the complexes mentioned, provide similar bonding patterns. There is a small decrease in the $CoP(P_3)$ bond overlap population from the triphos to the np_3 derivative, due to unfavorable mixing of the metal 4s orbital, which might be related to the small (mean) elongation observed for such distances in the np_3 complex.

In the series of $[(triphos)M(\eta^3\text{-}P_3)]$ compounds (M = Co, Rh, Ir) the PP distances increase a little (2.141 Å to 2.159 Å) on going from the 3d to the 5d metal complex. Both the $MP(P_3)$ and the MP(triphos) distances increase noticeably (*ca.* 0.11 Å) from the cobalt to the rhodium compound. Although such distances change only little on proceeding from the rhodium to the iridium compound as a consequence of the lanthanoid contraction, they however exhibit the following interesting trend: while the $MP(P_3)$ bonds lengthen by *ca.* 0.02 Å, those formed by the triphos donor atoms shorten by a corresponding amount. An analogous trend is observed for the two cationic Pd and Pt complexes (*cf.* Table 1) even though each differs from the corresponding neutral compound in having longer (*ca.* 0.07 Å) MP(triphos) distances.

Such a trend is indicative of competing conformational preferences of the two conical fragments—(triphos)M and $M(P_3)$—having their apices at the metal atom position. Which conformation is preferred should in turn be determined by properties of the metal atom, *e.g.* the size and energy of its valence orbitals, which do not vary linearly on going from first to third transition series[23]. It has been verified using the approximate atomic parameters available[23] that the important $\langle d(M)|P(P_3)\rangle$ overlap integrals do not vary linearly with the principal quantum number of the d orbitals, but reach a maximum for M = Rh. However, detailed conclusions on the origin of the above structural trend may hardly be drawn, because of the large number of possible factors involved and uncertainty in the values of parameters to be used in the calculations. As a final note, the extremely short PP distances (average 2.115 Å) in the palladium complex cation (*cf.* Table 1) again point to the importance of the electronic requirements of the individual metal atoms.

3.4. Electronic Spectra

The lowest-energy transition which is observed in the electronic spectrum of $[(triphos)Co(\eta^3\text{-}P_3)]$, *i.e.* before the onset of CT bands, is a shoulder at *ca.* 24000 cm^{-1}. With reference to Figure 5b, such a transition provides an estimate of the separation between the $2e\text{-}3a_1$ group of energy levels and the excited 4e level. In addition to this transition, a shoulder at lower wavenumber (20400 cm^{-1}) appears in the spectrum of $[(np_3)Co(\eta^3\text{-}P_3)]$. This could be due to small alterations in the pattern of energy levels caused by the lower "pyramidality" of the $(np_3)Co$ moiety relative to (triphos)Co, or to a contribution of the uncoordinated nitrogen atom to the axial ligand field strength in the np_3 derivative. As noted in the previous section, however, neither of these effects is indicated by the approximate calculations. As expected on consideration of the increasing ligand field strength, there is a high-energy shift of the bands on going from the cobalt to the rhodium complex (27000 cm^{-1}); in the spectrum of the iridium com-

[*] This electron partitioning is based on the concept of a closed-shell 18-electron configuration which, in general, cannot be readily reconciled with a delocalized MO picture of the bonding in the compound. In the present case, however, nine doubly occupied MO's which are mainly responsible for the closed-shell environment of the metal atom, may be identified: the 3e and $3a_1$ orbitals in Figure 5b, having predominantly metal character, the $1a_1$ and 2e orbitals, having metal and $\pi(P_3)$ contributions, and a set of three orbitals, not shown in the figure, mainly consisting of the phosphane "lone pairs".

pound no transitions are observed before the CT bands at *ca.* 28000 cm^{-1}. An analogous trend is exhibited by the spectra of the cationic derivatives, that of the Pd complex having a shoulder at 22600 cm^{-1} and bands in the region 25500–28500 cm^{-1}, whereas that of the Pt complex shows no bands below 28000 cm^{-1}[30].

4. Triple-Decker Sandwich Complexes of *cyclo*-Triphosphorus and *cyclo*-Triarsenic Ligands

4.1. Syntheses and Structures

The dinuclear triple-decker sandwich complexes containing the *cyclo*-triphosphorus group as ligand, or in some cases the *cyclo*-triarsenic group, have been obtained up to now by the following procedures:

a) By allowing stoichiometric amounts of P_4 (or As_4), the hydrated metal salt, and the phosphane ligand to react in solution. THF solutions of P_4 (or As_4) and of the ligand have generally been used, the hydrated metal salt being dissolved in ethanol. By this procedure only symmetric, *i.e.* having identical halves of the sandwich, triple-decker sandwich compounds are obtained.

b) By allowing a mononuclear complex [(triphos)M(η^3-P_3)] (M = Co, Rh, Ir) to react with a hydrated metal salt or metal complex in solution, in presence of the phosphane ligand. All reactants are generally dissolved in dichloromethane, except for the hydrated metal salts, which are dissolved in ethanol. In this way both symmetric and asymmetric complexes are obtained. In the latter, the metal atoms and/or the external ligands may be different.

c) By reducing the dinuclear *cyclo*-P_3 complexes described in a) or b), *e.g.* with $NaBH_4$ in acetone/ethanol.

If equimolar amounts of $[Co(H_2O)_6](BF_4)_2$ (or $[Ni(H_2O)_6](BF_4)_2$), the triphos ligand, and white phosphorus are allowed to react as described in procedure a), the complexes [(triphos)M-μ-(η^3-P_3)M(triphos)]$(BF_4)_2$ (M = Co, Ni) are isolated[11]. Their BPh_4 salts, which are generally suitable for structural investigations[11,31], were obtained by recrystallization from acetone/butanol, after adding $NaBPh_4$ to acetone solutions of these complexes. The *cyclo*-triarsenic derivatives [(triphos)M-μ-(η^3-As_3)M(triphos)]X_2·solvent (M = Co, Ni; X = BF_4, BPh_4) were analogously obtained using a solution of As_4 in THF[11,32]. Finally, the dinuclear palladium complexes [LPd-μ-(η^3-P_3)PdL]X (L = np_3, X = BF_4; L = triphos, X = BPh_4) were prepared by reaction of $[PdCl_2PBu_3]_2$ with white phosphorus in presence of the appropriate ligand L[15].

Following procedure b), the triple-decker sandwich complexes [(triphos)Co-μ-(η^3-P_3)M(triphos)]$(BPh_4)_2$·solvent (M = Co, Ni) are obtained by allowing the mononuclear cobalt complex [(triphos)Co(η^3-P_3)] to react with equimolar amounts of $[Co(H_2O)_6](BF_4)_2$ (or $[Ni(H_2O)_6](BF_4)_2$) and triphos, followed by addition of solid $NaBPh_4$[11]. By allowing [(triphos)Co(η^3-P_3)] to react with hydrated salts of divalent metals in presence of the alkyl-substituted tertiary phosphane 1,1,1-tris(diethylphosphinomethyl)ethane ($CH_3C(CH_2PEt_2)_3$, etriphos), mixed-ligand complexes [(triphos)Co-μ-(η^3-P_3)M(etriphos)]X_2 (M = Fe, Co or Ni, and X = PF_6 or BPh_4)[33] have been synthesized. In this manner, the iron-cobalt compound, a triple-decker complex with 30 valence electrons could be obtained[*].

Reaction of the rhodium complex [(triphos)Rh(η^3-P_3)] with hydrated metal salts and triphos affords the triple-decker heterometallic complexes [(triphos)Rh-μ-(η^3-P_3)M(triphos)]X_2·solvent (M = Co or Ni, and X = BF_4 or BPh_4)[34,35], which contain metal atoms of different transition-metal series. The above mononuclear rhodium complex also reacts with $[Rh(C_2H_4)_2Cl]_2$ (or $[Rh(CO)_2Cl]_2$) to yield the symmetric dirhodium derivative [(triphos)Rh-μ-(η^3-P_3)Rh(triphos)]BPh_4·$(CH_3)_2CO$[35]. Finally, starting from [(triphos)Ir(η^3-P_3)] the mixed iridium-cobalt complex [(triphos)Ir-μ-(η^3-P_3)Co(triphos)]$(BF_4)_2$·CH_2Cl_2 was obtained analogously[35].

The mononuclear educt complexes acting as synthetic building blocks in procedure b) were incorporated, undecomposed, into the dinuclear product complexes. Such behavior may be due on the one hand to efficient shielding of the η^3-P_3 core by the phenyl groups of the triphos ligand, which imposes constraints on the reaction path in such a way that disruptive transformations of the initial compound are prevented. On the other hand, the *cyclo*-P_3 phosphorus atoms are readily attacked, since they have considerable electron density in energetically accessible orbitals, and, in addition, have vacant orbitals at relatively low energies. It should also be noted that no change in the mean oxidation number of the metal atoms involved in the above synthetic processes occurs. In this respect formation of dinuclear complexes by procedure b) shows similarities to formation of the P_4 adducts, discussed in Section 2.1. On the other hand, it differs considerably from reactions of type a), in which redox processes invariably occur and the molecule of the P_4 reactant fragments.

Many of the triple-decker complexes can be oxidized or reduced, to some extent without decomposition. The complexes [(triphos)M-μ-(η^3-E_3)M(triphos)]BPh_4 (M = Co, Ni; E = P, As) have indeed been obtained by reduction of the corresponding dicationic compounds with $NaBH_4$[11]. This has been classified above as procedure c) for preparation of the triple-decker sandwich complexes. Redox processes in solution have been also performed on some of these compounds by cyclic voltammetric techniques[36], as is briefly described in Section 4.3.

All of the triple-decker complexes are stable in the solid state; most of them are also stable in solution, the exceptions being essentially due to the unsymmetrical compounds formed by two metal atoms of different transition-metal series. The nickel-rhodium complex, having VEN = 32 and low-lying excited states (see below) is particularly unstable.

In all of these triple-decker complexes the external "layers" are formed by the triphos, etriphos, or np_3-ligands, whereas the internal layer is formed by the *cyclo*-P_3 or *cyclo*-As_3 group. Each metal atom is bonded to the three phosphorus atoms of one external ligand and to the three

[*] The triple-decker sandwich complexes are assigned a valence-electron number (VEN) by straightforward extension of the criteria specified in Section 3.2 for mononuclear complexes, *e.g.*, the cobalt-nickel dication complex has VEN = 32 and the nickel-nickel monocation complex, described below, has VEN = 34.

atoms of the bridging η^3-E_3 group in a very distorted six-coordinate arrangement. A typical example is provided by the structure of the dication in the complex [(triphos)Ni-μ-(η^3-P_3)Ni(triphos)]$(BPh_4)_2 \cdot 2.5(CH_3)_2CO$, shown in Figure 6. Actually, four complexes out of a total of eight compounds of this type whose structures have been determined are isomorphous to the nickel complex:

[(triphos)Co-μ-(η^3-P_3)Co(triphos)]$(BPh_4)_2 \cdot 2CH_2Cl_2$[31]
[(triphos)Co-μ-(η^3-P_3)Ni(triphos)]$(BPh_4)_2 \cdot 2(CH_3)_2CO$[11]
[(triphos)Co-μ-(η^3-P_3)Rh(triphos)]$(BBh_4)_2 \cdot 2(CH_3)_2CO$[35] and
[(triphos)Co-μ-(η^3-As_3)Co(triphos)]$(BPh_4)_2$[11]

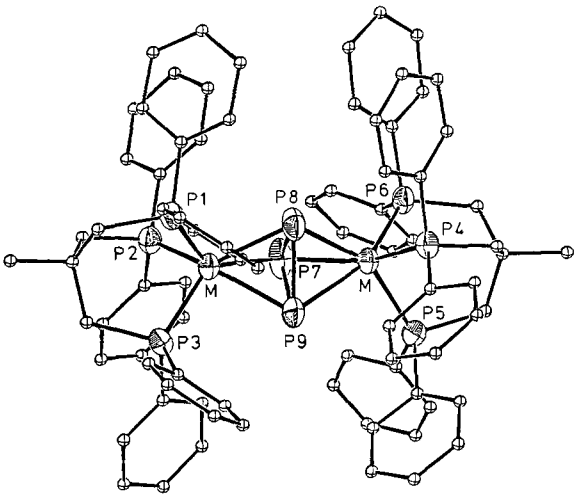

Fig. 6. Perspective view of the [(triphos)Ni-μ-(η^3-P_3)Ni(triphos)]$^{2+}$ cation (M = Ni) in the crystal.

Although the dication in each of these compounds has no crystallographic symmetry, its inner skeleton closely approaches C_3 symmetry. As shown in Figure 7a, the external ligands are rotated from the eclipsed position by *ca.* 30° about the pseudothreefold axis, whereas the phosphorus atoms forming the "inner triangle" are almost eclipsed

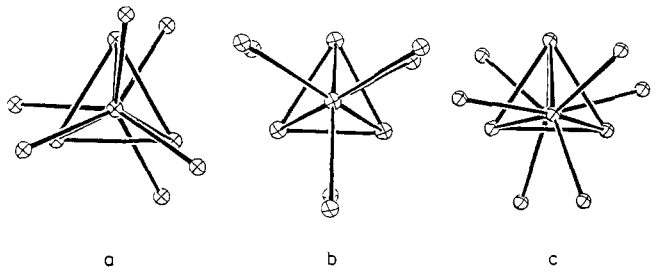

Fig. 7. Views along the molecular axis of the $P_3MP_3MP_3$ inner skeletons of representative triple-decker complexes: a) [(triphos)-Ni-μ-(η^3-P_3)Ni(triphos)]$^{2+}$; b) [(triphos)Pd-μ-(η^3-P_3)Pd(triphos)]$^+$; c) [(triphos)Ni-μ-(η^3-P_3)Rh(triphos)]$^{2+}$.

with those of one of the external layers. The inner coordination geometry in the cation of [(etriphos)Fe-μ-(η^3-P_3)Co(triphos)]$(PF_6)_2 \cdot CH_2Cl_2$[33] (Fig. 8) is closely similar to that of the above complexes, even though this iron-cobalt compound is not isomorphous to these. The [LPd-μ-(η^3-P_3)PdL]$^+$ (L = triphos, np_3) complexes have so far provided the only examples of a more regular arrangement[15,30] having the inner layer staggered with respect to the outer layers, so that the coordination geometry about each metal atom is a distorted octahedron (Fig. 7b). The nitrogen atoms of the two np_3-ligands in the cation

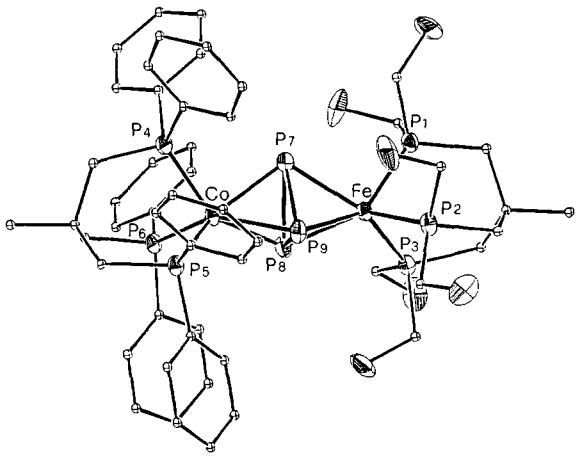

Fig. 8. Perspective view of the [(etriphos)Fe-μ-(η^3-P_3)Co(triphos)]$^{2+}$ cation in the crystal.

[(np_3)Pd-μ-(η^3-P_3)Pd(np_3)]$^+$ containing 34-valence electrons are uncoordinated (Fig. 9) and lie at 3.32 Å (average) from the metal atoms[30]. Finally, the structure of [(triphos)Ni-μ-(η^3-P_3)Rh(triphos)]$^{2+}$ shows significant deviations from the idealized C_3 symmetry[35]. In particular, the *cyclo*-triphosphorus group in such a complex forms an isosceles triangle, whose centroid is displaced away from the line joining the two metal atoms, with the vertices of the triangle lying in a plane perpendicular to this line (Fig. 7c). Relevant structural data for the above dinuclear complexes are listed in Table 2. Detailed consideration of the most significant features of these structures will be undertaken in the light of the following section on the bonding in these compounds in Section 4.4.

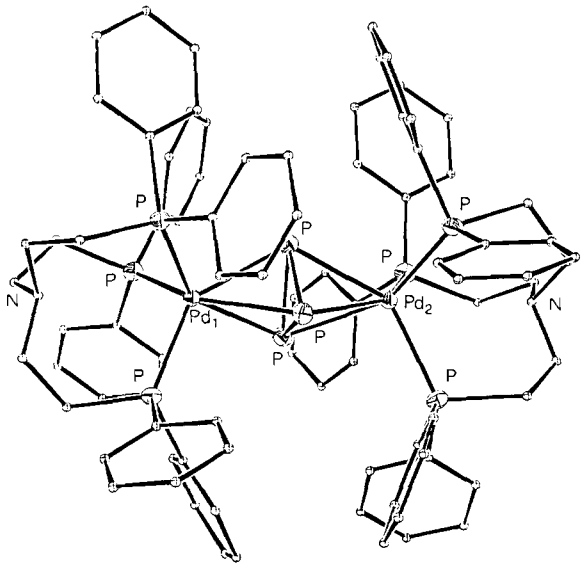

Fig. 9. Perspective view of the [(np_3)Pd-μ-(η^3-P_3)Pd(np_3)]$^+$ cation in the crystal.

Table 2. Structural data for the triple-decker sandwich complexes [LM-μ-(η^3-E_3)M'L']$^{n+}$ [a, b].

Comp.	M,M'	VEN	Distances MP(L,L')	ME	MM'	EE	Angles PMP [c]	EME	Ref.
1	Fe,Co	30	2.20	2.29	3.80	2.23	91.4	58.1	[33]
2	Co,Co	31	2.23	2.31	3.86	2.18	93.5	56.3	[31]
3	Co,Ni	32	2.24	2.33	3.93	2.16	93.4	55.3	[11]
4	Ni,Ni	33	2.25	2.35	3.99	2.16	94.7	54.7	[11]
5	Co,Rh	31	2.22	2.31	3.87	2.20	92.9	56.7	[35]
6	Ni,Rh	32	2.21–2.34	2.31–2.56	4.04	2.15–2.31	88–95	52–59	[35]
7	Pd,Pd	34	2.38	2.50	4.33	2.14	92.0	50.7	[15]
8	Co,Co	31	2.22	2.41	3.91	2.43	92.0	60.8	[11]

[a] L = etriphos, L' = triphos: **1**; L = L' = triphos: **2–8**; E = P: **1–7**; E = As: **8**. [b] Averages over chemically equivalent bond distances [Å] and angles [°] are reported (except for the highly distorted compound **6** assuming M = M' for the heterometallic dications due to disordering (**3**, **5**) or to close similarity in coordination about the two metal centers **1**; standard deviations, calculated as in Table 1, are typically less than 0.01 Å and 1°, respectively. [c] Angles between P atoms of L and L'.

4.2. MO approach to the Bonding

The essentials of the orbital correlation diagram for a [LM-μ-(η^3-P_3)ML]$^{n+}$ model compound are shown in Figure 10. Although it is derived for idealized D_{3h} symmetry, in which adjacent layers are mutually staggered, it applies with only minor alterations, noted below, to the C_3 effective symmetry possessed by the majority of triple-decker complexes. The energy levels of the two LM fragments, separated by rather large distances of 3.8–4.3 Å, are shown on the left-hand side (Fig. 10a): the groups of orbitals originating from the upper- and lower-d blocks, and from the higher-lying sp hybrid orbital of an LM monomer fragment are readily identified. The important orbitals of the *cyclo*-P_3 group are sketched on the right-hand side (Fig. 10c). Valence orbitals of the dinuclear model compound appear in Figure 10b, with the occupancy appropriate for the VEN value of 33, which corresponds to the nickel-nickel dication.

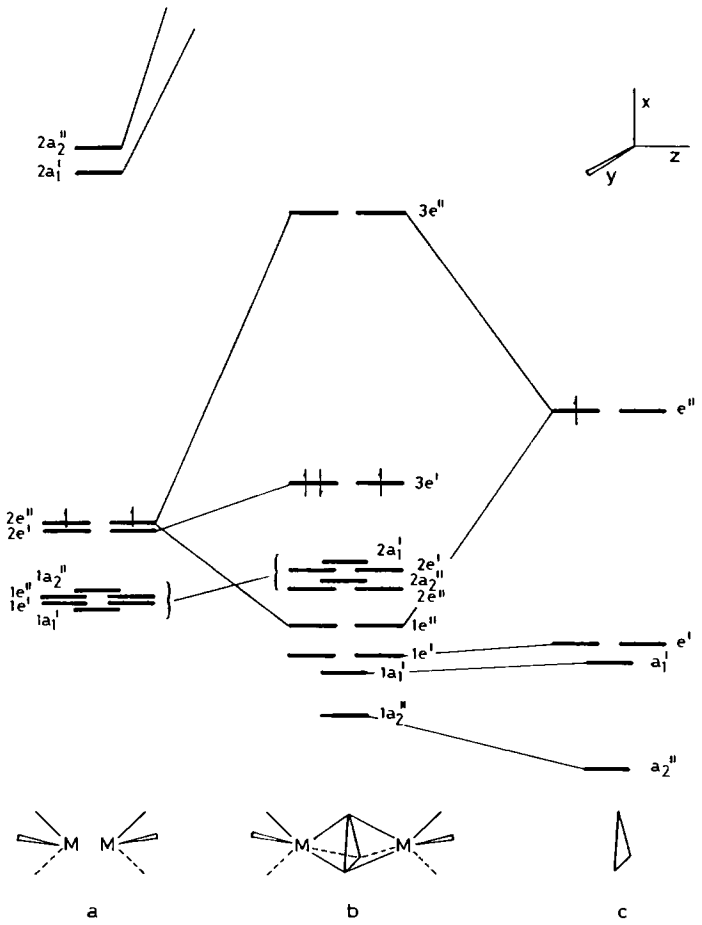

Fig. 10. MO correlation diagram for [LM-μ-(η^3-P_3)ML]$^{n+}$ complexes (D_{3h} symmetry); a, b, c see text.

The principal stabilizing interaction involves the metal xz and yz orbitals, which contribute to both e'' combinations of the LM...ML system, and the phosphorus z orbitals forming the e'' set of the *cyclo*-P_3 fragment. The occupied orbitals resulting from this interaction form the 1e'' set in Figure 10b. Interactions between the metal orbitals and those lying in the plane of the *cyclo*-P_3 group become more and more important as the distance between the two LM fragments decreases below *ca.* 3.8 Å. In particular, the cluster of the essentially metal 2e''-2a$_1'$ orbitals spreads considerably with decreasing M...M separation, whereas the 1a$_1'$ and 1e' combinations, predominantly localized in the plane of the *cyclo*-P_3 unit, are stabilized. The energies of all these orbitals are also affected by rotating the LM and P_3 molecular fragments about the threefold axis. The 3e' set forming the HOMO in most of these complexes has antibonding character in the interactions between the metal d orbitals and those of the phosphorus atoms lying in the plane of the *cyclo*-P_3 group. At the MM separation in the nickel-nickel dication, 76% metal and 12% *cyclo*-P_3 contributions to the HOMO are indicated by SCCC calculations in qualitative agreement with the electrochemical data.

4.3. Magnetic Properties and Redox Behavior of the Complexes

The redox behavior of the triple-decker sandwich complexes has been investigated electrochemically[36]. The reversible three-step cyclic voltammogram of the dicobalt complex [(triphos)Co-μ-(η^3-P_3)Co(triphos)](BF$_4$)$_2$ shown in Figure 11 indicates that a one-electron oxidation and two one-electron reduction processes may be performed on the 31-electron starting compound in acetonitrile. Therefore the range of VEN values from 30 to 33 is spanned by removing or adding electrons to the 3e' orbitals in the diagram in Figure 10. The diamagnetic bright green [(triphos)Co-μ-(η^3-P_3)Co(triphos)]$^{3+}$ species has been generated in solution by bulk oxidation of the dication at a controlled potential[36].

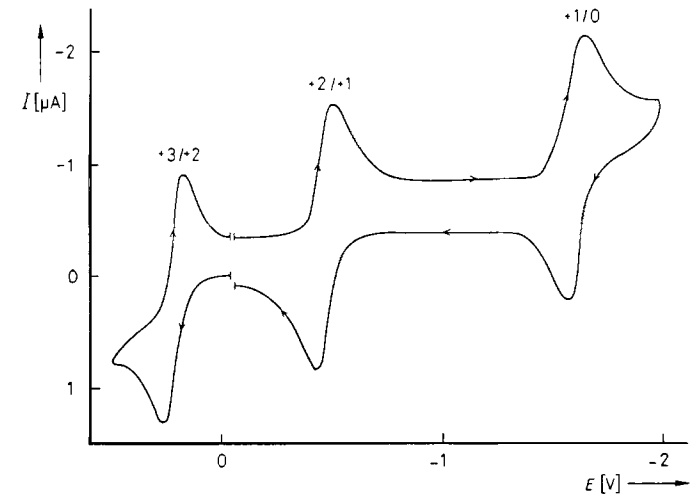

Fig. 11. Cyclic voltammogram of [(triphos)Co-μ-(η^3-P_3)Co(triphos)]$(BF_4)_2$: potential relative to Ag/Ag^+ (0.01 M).

The electrode potentials of the [(triphos)M-μ-(η^3-E_3)M(triphos)]$^{2+}$ (M = Co, Ni; E = P, As) complexes, reported in Figure 12, show that: a) oxidation processes occur at higher potentials for the nickel complexes than for the cobalt ones, in agreement with the trend in metal ionization potentials, which are of course embodied in the parameters used in the semiempirical calculations[23], and b) *cyclo*-As_3 complexes are more readily oxidized than the *cyclo*-P_3 derivatives. The latter result, being in accord with the expected trend from atomic ionization energies of group V atoms, indicates that the nature of the HOMO is influenced to some extent by that of the *cyclo*-E_3 unit.

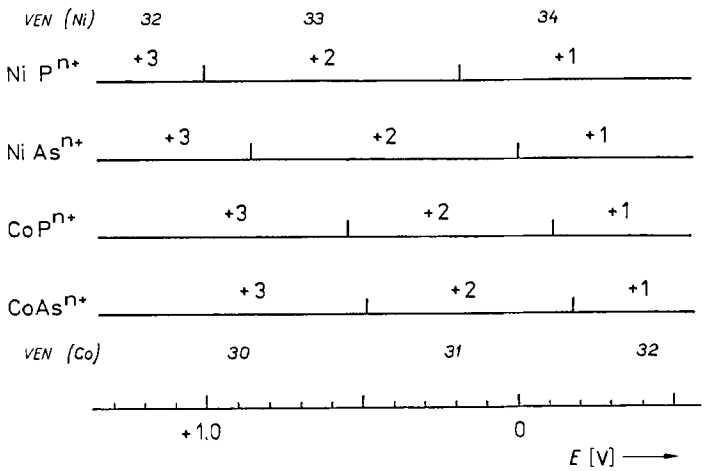

Fig. 12. Electrode potentials for the redox transitions of triple-decker sandwich complexes (*e.g.*, NiP^{n+} in the figure stands for [(triphos)Ni-μ-(η^3-P_3)Ni(triphos)]$^{n+}$, *etc.*). VEN = number of valence electrons; potential measured relative to saturated calomel electrode (SCE).

The magnetic properties of the triple-decker sandwich complexes formed by 3d metal atoms can be rationalized as follows: a) The 3e′ level is separated by large energy gaps both from the lower levels and from the successive 3e″ level. The electronic spectra suggest that the first of these energy separations is probably underestimated by the approximate calculations, or is an unsuitable indicator of the separation between the actual molecular states originating from the one-electron configurations; b) the 3e′ doubly-degenerate level is either empty, or completely filled, respectively, in the diamagnetic triple-decker sandwich complexes having VEN = 30 or 34; c) the 3e′ set is progressively occupied in paramagnetic complexes with VEN ranging from 31 to 33, which have a doublet (VEN = 31 or 33), or a triplet ground state (VEN = 32).

The magnetic behavior of 32-electron complexes formed by 4d or 5d metal atoms, such as the distorted nickel-rhodium derivative (Fig. 7c), deviates from the general trends; it is considered in more detail in Section 4.6.

4.4. Structural Features

Before examining the possible trends revealed by the structural data listed in Table 2 for these triple-decker sandwich complexes, it has to be noted that in the lattices of all the heteronuclear compounds investigated so far (except for the iron-cobalt compound having a highly asymmetric cation, cf. Fig. 8) the position of the complex cation is affected by twofold orientational disorder, so that each metal site is populated with almost equal probability by each of the metal atoms. Therefore, in these structures only average values of bond distances and angles about the two metal centers have been measured.

From the data listed in Table 2 it appears that in the series formed by the iron-cobalt, cobalt-cobalt, cobalt-nickel, and nickel-nickel dications, which are 3d complexes with VEN increasing along the series from 30 to 33, both the $MP(P_3)$ and MP(L) distances increase smoothly from 2.29 Å to 2.35 Å, and from 2.20 Å to 2.25 Å, respectively (the MM distances correspondingly increase from 3.80 Å to 3.99 Å). It should be noted that such trends are the opposite to those expected on the basis of the variations in the metal atom radii. The PP distances in the *cyclo*-P_3 group on the other hand exhibit the opposite trend, decreasing from 2.23 Å to 2.16 Å as VEN increases from 30 to 33. Moreover, this reduction is not linear, since the contraction between VEN = 30 and VEN = 32 is greatest.

The increase in the $MP(P_3)$ distances with increasing VEN values is evidently related to the antibonding character of the HOMO with respect to such MP interactions. Trends in the other distances are, however, less easily rationalized, due to the large number of potentially effective interactions. SCCC calculations using a fixed geometry were used for the model complexes (VEN = 30—33, dicationic; VEN = 34, monocationic), and indicated that the overlap populations of *all* MP bonds decrease, whereas those of the PP bonds increase slightly with increasing VEN. Such results are consistent with the observed structural trends but cannot be readily traced to a few dominant interactions, except for the variation in the $MP(P_3)$ distances. Complementary information has been obtained by calculations in which both the LM...ML and the PP distances were systematically varied. They indicated that a decrease in the MM distance entails a considerable increase in valence-orbital antibonding interactions between the metal atoms and the *cyclo*-P_3 group. Such interactions are somewhat relieved by an increase in the size of the η^3-P_3 ring. This may provide a rationalization for the trend in the PP distances if the contraction of the $MP(P_3)$ bonds

with decreasing VEN is assumed to be the dominant effect.

The distances between atoms of the *cyclo*-P_3 group in the dinuclear complexes (Table 2) are generally shorter, as are those in the mononuclear complexes, than the PP distance of 2.21 Å in the isolated P_4 molecule[18] (the distorted nickel-rhodium derivative[35] is not considered here). As already noted for the mononuclear complexes, a contraction of this type is probably due to a decrease in the antibonding interactions between the phosphorus atoms, rather than to a shift of electron density from the inner slice to the outer parts of the complex. The PP overlap population parallels the decrease in bond length, increasing by *ca.* 30% from the P_4 molecule to the *trihapto cyclo*-P_3 group bonded to one metal atom. It increases slightly in the dinuclear complexes relative to that in the mononuclear.

The mean AsAs distance of 2.43 Å in [(triphos)Co-μ-(η^3-As_3)Co(triphos)]$(BPh_4)_2$ (**8** in Table 2), matches that in the As_4 molecule[18] as well as that found for an organocyclotriarsane[37]. On the other hand it is longer than the distance of 2.372(5) Å found in $[As_3Co(CO)_3]$[27].

Triple-decker sandwich complexes formed by metal atoms of different transition series would be expected to exhibit appreciable differences in the bond lengths about the two metal centers. Although such differences have not been directly observed to date because of disorder in the lattice, it should have been possible to notice some of their effects, such as abnormal shapes of thermal ellipsoids of the atoms in the coordination sphere. However, anomalies of this type have not been detected (see compound **5** in Table 2). Focusing on the position of the inner slice in the complex, the above results suggest that this group may maximize its interactions with the outer fragments by lying closer to the heavier metal atom than would be expected by consideration of bond distances in the corresponding mononuclear complexes. Actually, calculations on a cobalt-rhodium model compound indicate that the minimum in the total energy for motion of the inner layer along the metal-metal axis lies close to the middle point of this axis (it is even slightly shifted toward the side of the heavier atom).

An interesting problem is posed by the conformation of the triple-decker sandwich complexes, since the orientation of the three slices is not unique for such compounds and in the most common conformation the three moieties are rotated with respect to each other about the molecular pseudo-threefold axis in an apparently random fashion.

The angles used to describe such rotations are defined in Figure 13. As already noted, the majority of complexes listed in Table 2 attain a conformation close to that shown in Figure 7a, with $\alpha \approx 30°$ and $\beta \approx 0°$, exceptions being complexes **6** and **7** (Table 2), whose inner skeletons are respectively sketched in Figures 7c and 7b.

Excluding lattice effects, because not all of the compounds with the arrangement shown in Figure 7a are isomorphous to each other, the possible factors determining the mutual orientation of the three slices are non-bonding interactions within the cation and electronic bonding effects.

There are indeed numerous close contacts between substituent groups on the phosphorus atoms of the outer ligands although none of the distances are very short. It has to be noted in this connection that the triphos ligand undergoes a conformational rearrangement going from the mononuclear to the dinuclear compounds, involving shifts of the phenyl groups (some carbon atoms are shifted by as much as 1 Å) away from the central part. While the above mentioned interactions probably determine the mutual orientation of the external layers (they may fix the angle α to *ca.* 30° not only in the five isomorphous compounds **2—5** and **8** listed in Table 2 but also in the nickel-rhodium derivative **6** which differs in other structural features: cf. Fig. 6 and Table 2), additional short contacts (<3.5 Å) between the atoms of the inner layer and the phenyl carbons

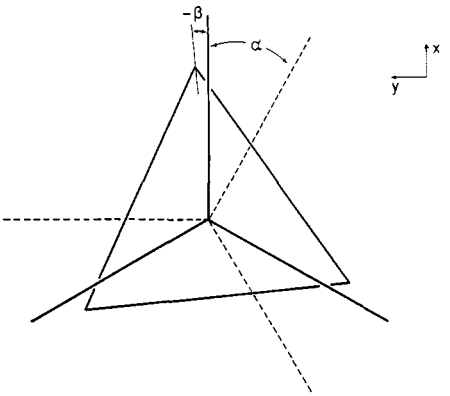

Fig. 13. Schematic representation along the pseudo-threefold axis of the inner skeleton of a triple-decker sandwich complex: angles α and β measure rotations of one on the outer layers and of the internal slice, respectively, from the reference position of the second outer layer.

in *ipso*-positions appear to fix the arrangement of all three slices. These interactions, in particular, should be responsible for the fact that the heteroligand dication [(etriphos)Fe-μ-(η^3-P_3)Co(triphos)]$^{2+}$ (Table 2), which has a short M...M′ distance, has the same conformation (Figs. 7a and 8) as the majority of the homoligand dications. The higher symmetry of the inner skeletons of the PdPd complexes (Figs. 7b and 9) may result from the absence of all above steric hindrances, caused in turn by the very long PdP distances (cf. Table 2).

The possible role of electronic factors in determining the conformation of the triple-decker sandwich complexes has been probed by a cursory examination of the barriers to rotation of the three fragments about the molecular axis in model compounds. In short, the arrangement with D_{3h} symmetry should be favored both in terms of total energy and of overlap populations of the MP bonds. The rotational barriers show a moderate and smooth increase with VEN, so that the conformation of a 34-valence electron complex, such as the dipalladium derivative, would not be expected to differ substantially from that of the other complexes on consideration of the electronic factors alone[*].

[*] The orbitals mostly affected by the rotations are those having large MP(L) character, in addition to those already mentioned, *i.e.* the $1a_1'$ and 1e′ orbitals (Fig. 10b) and the 2e″-2a′ orbitals of the d block. Considering that the "tilting" [21] of the highest-occupied degenerate orbitals of the ML fragments is partly removed in forming the dinuclear complex, and that purely π-type combinations do not set rotational barriers, it is not surprising that the most notable effects of the rotations are due to the closed-shell interactions between the MP(L) bonds and the *cyclo*-P_3 unit.

The height of the rotational barrier of the inner slice with fixed LM...ML framework decreases steadily with increasing values of α (Figs. 14a and 14b), becoming quite small for $\alpha = 60°$. Finally, the height and shape of the barriers are strongly dependent upon the orientation of the PH_3 groups of the model molecule about their MP axes (Fig. 14c), in such a way that it would be possible, by choosing appropriate orientations of such groups, to produce a minimum energy conformation matching the experimental one. The last result emphasizes that nonbonding interactions are more important than bonding effects in determining the geometry of the compounds. In particular, it suggests that in a more fundamental approach to this problem, the geometric requirements of the phosphane ligands should not be neglected.

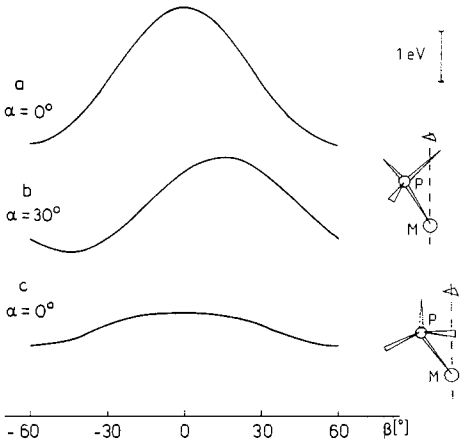

Fig. 14. Barriers to rotation of the *cyclo*-triphosphorus group, with fixed LM...ML frame, about the threefold axis in triple-decker sandwich complexes. The orientation of the PH_3 groups about the MP axes (see sketches at right: a) and b) 60° apart from c), is consistent with D_{3h} symmetry of the model molecule at $\alpha = 0°$.

4.5. Spectral Properties

The main features of the electronic spectra of the triple-decker sandwich complexes formed by 3d metals may be understood by firstly considering the spectra of the compounds with the "extreme" VEN values of 30 and 34. Bands lying in the region 11000—17000 cm^{-1} of the spectrum (Fig. 15a) of the only available 30e compound[33] should have substantial d-d character due to transitions from the 2e''-2a'$_1$ group of one-electron levels (Fig. 10b) to the 3e' level, which is the LUMO for this compound. On the other hand, the lowest-energy d-d bands (17000—22000 cm^{-1}) in the spectra of the 34e monocations[11] (a representative spectrum is shown in Figure 15c) should be assigned as 3e'→3e'' (such bands show a considerable high-energy shift going from the 3d to the 4d metal complexes)[30]. Both types of transitions are active for complexes with VEN in the 31-33 range, as may be verified by comparison of the spectrum in Figure 15b with those in Figures 15a and 15c and considering that a) the regions of the d-d spectrum containing bands of the above two types should only marginally overlap (Fig. 15a and 15c) and b) that both sets of transitions should shift to higher energies with decreasing VEN, due to the decrease in MP distances and the parallel increase in metal-ligand interactions.

$^{31}P\{^1H\}$-NMR spectra have been reported recently for the two triple-decker sandwich complexes [LPd-μ-(η^3-P_3)PdL]X (L = triphos, X = BPh_4; L = np_3, X = BF_4; VEN = 34) and for the mononuclear complexes [(triphos)M(η^3-P_3)]BF_4, with M = Pd, Pt[15]. The former exhibit

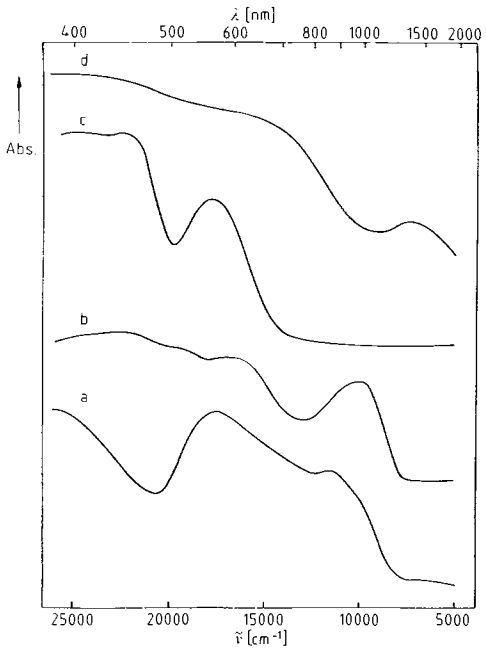

Fig. 15. Reflectance spectra of representative triple-decker sandwich complexes (VEN values in parenthesis):
a) [(etriphos)Fe-μ-(η^3-P_3)-Co(triphos)]$(PF_6)_2 \cdot CH_2Cl_2$ (30);
b) [(triphos)Ni-μ-(η^3-P_3)Ni(triphos)]$(BPh_4)_2 \cdot 2.5(CH_3)_2CO$ (33);
c) [(triphos)Ni-μ-(η^3-P_3)-Ni(triphos)]$(BPh_4) \cdot (CH_3)_2CO$ (34);
d) [(triphos)Ni-μ-(η^3-P_3)-Rh(triphos)]$(BF_4)_2 \cdot C_4H_8O$ (32).

an A_3X_6 pattern and the latter an A_3X_3 pattern. The large chemical shift of the *cyclo*-P_3 phosphorus atoms increases from the monometal to the dimetal complexes. The ^1J(M,P) value for the *cyclo*-P_3 phosphorus atoms is more than one order of magnitude smaller than that of the triphos P atoms. Such a reduction in going from σ-bonded to π-bonded systems is not unusual[15].

4.6. Properties of Complexes with VEN = 32

The spectral and magnetic properties of the 32e complexes containing at least one 4d or 5d metal atom, which have been synthesized to date, differ significantly from those of the isoelectronic complexes formed solely from 3d metals[35]. These "mixed" complexes have a singlet ground state, rather than the spin triplet which would be expected for the $(3e')^2$ configuration, or exhibit small residual paramagnetism. Moreover, bands at unusually low energies are present in their electronic spectra (Fig. 15d). Such properties have been correlated with the known structure of the nickel-rhodium dication, in the light of the proposed bonding pattern for the dinuclear complexes. Generalizing, it has been assumed[35] that the distortion which is observed (a stabilizing Jahn-Teller distortion in which the effective symmetry of the inner-skeleton is lowered from C_3 to C_2; cf. Fig. 7c) is caused by the higher field strength and larger spin-orbit coupling constants of the heavier metal

atom(s). Although EH calculations, which do not include the repulsive two-electron and higher terms in the Hamiltonian, are not expected to provide a definitive answer about this point, they do, however, give the following indication, partly consistent with the above hypothesis: the contributions to the highest-occupied MO's of the complex by the bridging phosphorus atoms increase considerably with the atomic number of the metal atoms (by *ca.* 100% from 3d to 4d metals), *i.e.* with increasing covalency. Such an increase is significant, because the *cyclo*-P_3 group has the greatest effect on the distortion (Fig. 7c). These complexes which even in the ground state are distorted, and the presence of low-lying excited states, revealed by the spectra, may account for the fact that their synthesis has proved so far to be rather elusive, that their magnetic properties are somewhat dependent on the nature of the counterion and even on the preparation of the sample, and that the complexes decompose rapidly in solution.

5. Adducts of Mononuclear *cyclo*-Triphosphorus Metal Complexes

As has already been stressed, the *cyclo*-P_3 unit bonded to one metal atom as a *trihapto*-ligand may form additional bonds to new metal atoms or to other centers with Lewis acid properties. In other words it imparts Lewis base properties to the mononuclear metal complexes. This property has been exploited to form triple-decker sandwich complexes from the mononuclear *cyclo*-P_3 derivatives (Section 4.1). The affinity of the monometal *cyclo*-P_3 complexes for electron-acceptor groups has moreover been tested by allowing than to react with metal carbonyls or related compounds.

The [(triphos)Co(η^3-P_3)] complex dissolved in THF reacts with solid $Cr(CO)_6$ under UV irradiation according to the following scheme:

$$[(\text{triphos})\text{Co}(\eta^3\text{-}P_3)] + n\,\text{Cr(CO)}_6 \xrightarrow{h\nu} [(\text{triphos})\text{Co}(\eta^3\text{-}P_3)]\{\text{Cr(CO)}_5\}_n] \quad (n = 1, 2)$$

The dinuclear or the trinuclear complex is obtained, depending on the stoichiometry and the conditions[7,38]. No compound with more than two $Cr(CO)_5$ groups attached to the *cyclo*-P_3 unit has been obtained by this procedure.

The structure of the [(triphos)Co(η^3-P_3)$\{Cr(CO)_5\}_2$] complex is shown in Figure 16. Bond distances within the *cyclo*-triphosphorus group are essentially unchanged relative to those in the parent compound[7]. The chromium atoms are displaced from the plane of the *cyclo*-P_3 unit on the opposite side to that of the cobalt atom, the two CrP bonds forming angles of *ca.* 65° and 70° with the normal to this plane. The CrP bond lengths, which fall in the range observed for such distances in phosphane-substituted chromium complexes, and the CO stretching frequencies are indicative of metal-phosphorus interactions comparable to those of phosphane complexes[7].

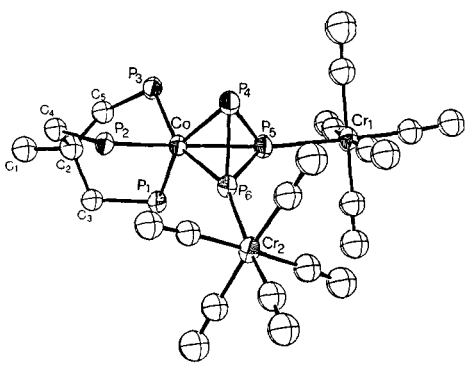

Fig. 16. Skeleton of the [(triphos)Co(μ-(η^3-P_3))$\{Cr(CO)_5\}_2$] molecule in the crystal.

A tetranuclear adduct, in which each phosphorus atom of the *cyclo*-P_3 unit of the parent [(triphos)Co(η^3-P_3)] complex is linked to a metal center, has been synthesized using a substituent group with similar electronic properties but lower steric requirements than pentacarbonylchromium. Hence [(triphos)Co(η^3-P_3)] reacts with $Mn(C_5H_5)(CO)_3$ in THF under UV irradiation to afford the [(triphos)Co(η^3-P_3))$\{Mn(C_5H_5)(CO)_2\}_3$] complex[39]. The structure of the compound is shown in Figure 17. The mean value of the PP distances in the tetrametal complex is practically unchanged relative to the parent compound. The MnP bonds are tilted from the plane of the *cyclo*-P_3 unit essentially by the same amount on average as the CrP bonds in the previous trimetal complex.

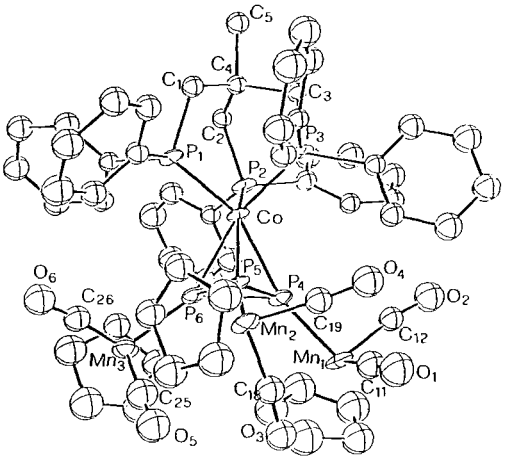

Fig. 17. Perspective view of [(triphos)Co(η^3-P_3))$\{Mn(C_5H_5)(CO)_2\}_3$] in the crystal.

Calculations at the EH-SCCC level performed on a [LCo(η^3-P_3))Cr(CO)$_5$] model compound have indicated that the bonding pattern in the valence-orbital region is not considerably modified from that of the original cobalt complex, because the electronegative $Cr(CO)_5$ fragment has relatively low-lying occupied orbitals available for interaction. This allows the diamagnetism of the dichromium and trimanganese adducts and their spectra, which are similar to those of the mononuclear cobalt complexes (bands characteristic of the appended chromophores are expected to occur in the CT region in the spectra of the polymetal species) to be rationalized. In spite of the fact than an additional strong bond is formed in the model compound between a *cyclo*-P_3 phosphorus atom and the new metal center (the overlap population of the CrP bond is practically identical to that of a CoP(L) bond) and that an overall shift of electron density takes place toward the chromium moiety, the mean value of the PP overlap popu-

lation is almost identical to that calculated for the parent compound. No optimization of the geometry was performed in the above calculation. A separate set of calculations in which the angle between the CrP bond and the threefold axis of the cobalt fragment was varied yielded a minimum-energy conformation essentially matching the experimental one. It therefore appears that the arrangement of the attached groups in these polymetal adducts is determined by electronic factors, rather than by steric effects.

A very recent result is the synthesis of the heterometal triple-sandwich complex [(triphos)Co(P_3)($CuBr)_6$(P_3)Co(triphos)], formed by allowing a solution of [(triphos)Co(η^3-P_3)] in dichloromethane to react with a suspension of CuBr[40]. The internal slice in such compounds, formed by a hexagon of copper atoms bridged in pairs by bromine atoms, is sandwiched by the *cyclo*-P_3 groups of the two external (triphos)Co(P_3) units (Fig. 18). The inner core may be alternatively described as a cuboctahedron of six copper and six phosphorus atoms.

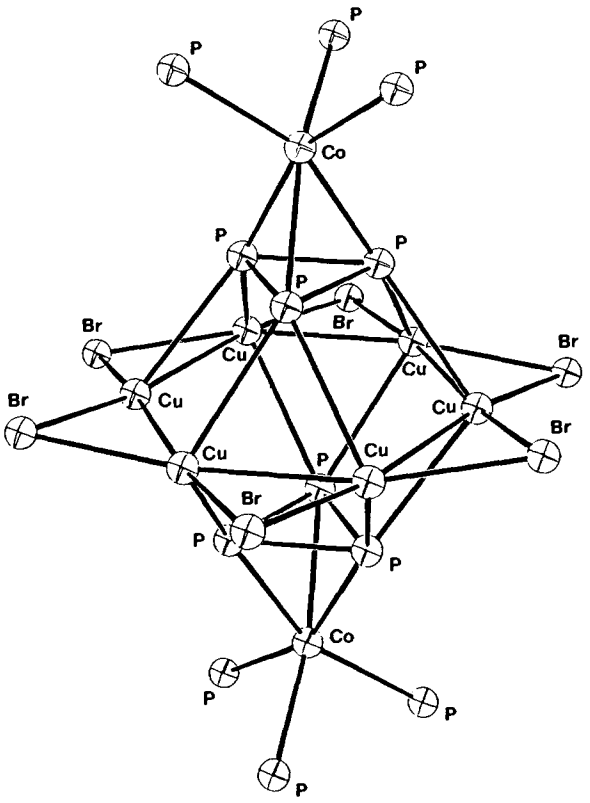

Fig. 18. Skeleton of [(triphos)Co(P_3)($CuBr)_6$(P_3)Co(triphos)] in the crystal.

It is evident that in spite of the work already performed in this field, much has still to be done. In particular, the mechanisms of the most important processes are still obscure. On the synthetic side, the chemistry of additions at η^3-coordinated *cyclo*-triphosphorus units is an open field, possible limitations to the nature of products probably arising only from the geometric constraints imposed by the "ancillary" phosphane ligands.

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Topical Problems in the Biosynthesis of Red Blood Pigment**

By Burchard Franck*

Uroporphyrinogen III plays a key role in the biosynthesis of heme, the red pigment of blood. *In vivo* studies with specifically ^{14}C- and ^{3}H-labeled precursors have revealed that the formation of uroporphyrinogen III in the organism follows several primary and subsidiary pathways. Model experiments on the pattern of biosynthesis have led to simple and effective methods of synthesizing uroporphyrin analogs and have shown that their production is strongly favored thermodynamically. The biologically important porphyrins thus available permit a mechanistic explanation of the light-induced dermatoses in porphyria diseases and suggest promising medical applications in diagnosis and therapy.

1. Introduction

Each cubic centimeter of human blood contains 5 billion erythrocytes (Fig. 1), the most important component of which is the conjugated protein hemoglobin. The five liters of blood circulating within the body of an adult contain almost one kilogram of hemoglobin, which can bind and transport 1.3 liters of oxygen. The red blood pigment heme **1** can be cleaved off hemoglobin by acid hydrolysis. The human body contains some 30 g of heme, which is renewed by biosynthesis within a period of 120 days.

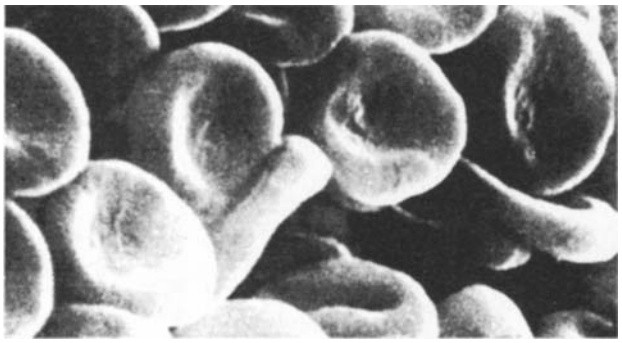

Fig. 1. Human erythrocytes in a scanning electron microscope (magnification about 4000) (from [1]).

Thus, every year the world's human population biosynthesizes some 400000 tons of heme, this being almost equal to the annual global industrial production of organic dyes. Because of the vital functions of heme, its biosynthesis—a process controlled by a large number of enzymes—occupies a central position in the body's metabolism[2].

Research into heme biosynthesis has enabled

1) the key biogenetic compounds to be pinpointed
2) simple biomimetic syntheses to be developed, and finally
3) some metabolic diseases to be understood and treated.

Re 1: The key biogenetic compounds—themselves produced by fairly simple enzymatic reactions—are the precursors for the biosynthesis of a large group of other natural products[3].

Re 2: By following the biosynthetic pattern, particularly simple and effective laboratory syntheses of complicated natural products can often be developed[4]. Such "biomimetic syntheses" need not be performed under the exact conditions of the biosynthesis[*].

Re 3: The principal biogenetic compounds are the nodes or junctions in the network of metabolic pathways. Any disturbance in the formation or conversion of these compounds leads to the development of metabolic diseases, *e.g.* porphyrias are caused by disturbances in heme biosynthesis[5-7].

The discussion that follows will be centered around the above three points. Our current understanding of heme biosynthesis will first be outlined, with special consideration of the key biogenetic compounds. This will be followed by a description of applications of this knowledge in organic chemistry and medicine.

2. The Biosynthesis of Heme

The basic skeleton of the red blood-pigment heme **1** is termed porphyrin **2**, a stable, cyclically conjugated [18]annulene system. Under the influence of mild reducing agents the deep-red porphyrins can be converted into the colorless porphyrinogens **3** *via* addition of six H atoms. Porphyrinogens are more reactive than porphyrins, atmospheric oxygen, for example, being sufficient to dehydrogenate them back to porphyrins.

Approximately 30 biologically active, cyclic tetrapyrroles of the porphyrin type are now known; as far as man is concerned, apart from heme, the cytoheme of the cytochromes and the chlorophylls are the most important compounds[8]. Considering its comparatively complex structure, it is astonishing that heme is produced in the body from two very simple building blocks, glycine **5** and succinic acid **4**[9,10]. Because of their methodological origi-

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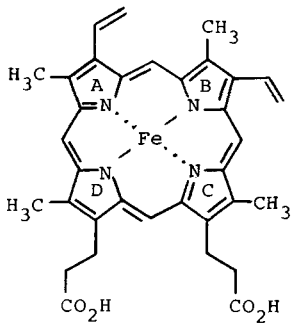
[**] Based on a plenary lecture (Richard Kuhn Memorial Lecture) given in Tübingen on March 24, 1981 on the occasion of the Chemiedozenten-Tagung.

[*] "Biomimetic chemistry is the branch of organic chemistry which attempts to imitate natural reactions and enzymatic processes as a way to improve the power of organic chemistry" (*Breslow* [4d]).

nality and impact, this discovery and the clarification of the subsequent course of the condensation by *Shemin et al.* rank among the greatest pioneering achievements of biosynthetic research, and have never been disputed[9,4c].



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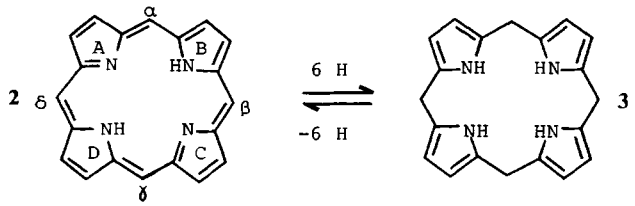
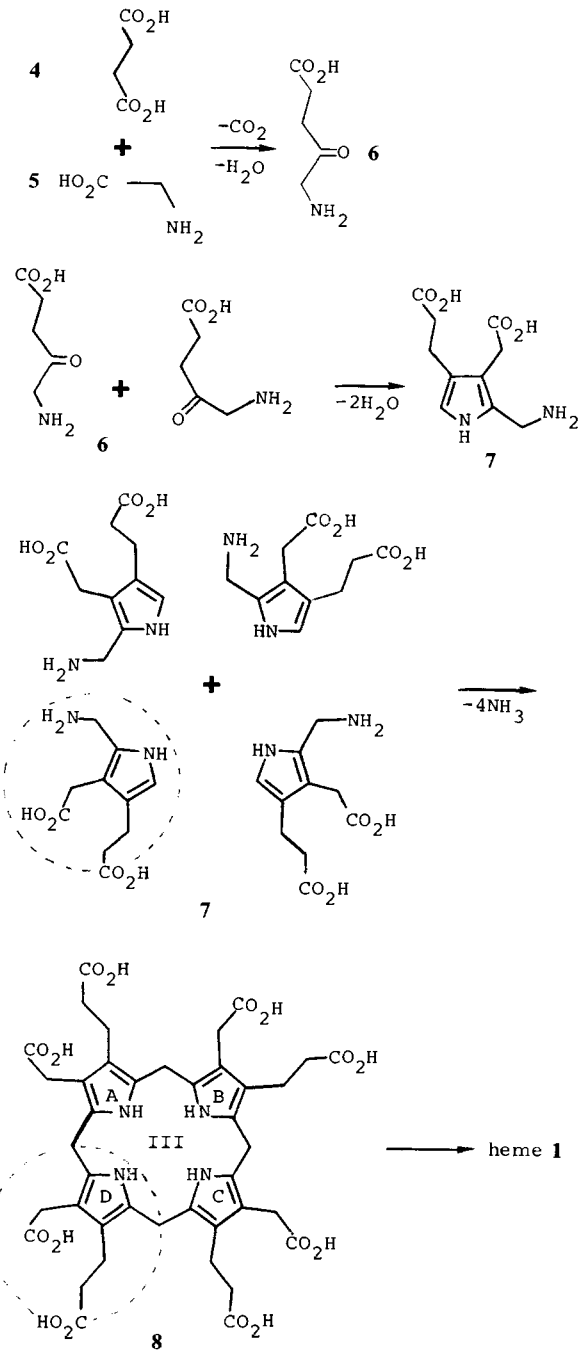


2 **3**

Shemin started with the incorporation of [^{15}N]glycine into his own bloodstream and subsequently devised a reliable method using hemolyzed duck blood. He was thus able, as long as 35 years ago, to describe accurately the biosynthesis of the heme molecule from eight molecules of glycine **5** and eight of succinic acid **4**. **5** and **4** first condense *via* decarboxylation to form 5-aminolevulinic acid **6**, two molecules of which condense further to form the monopyrrole compound porphobilinogen **7**[25]. With the release of ammonia, four porphobilinogen units next combine to afford uroporphyrinogen III **8**. For a long time the clarification of heme biosynthesis went no further than this stage, because little promise was seen in radioactively labeling a compound as large and complicated as **8** and exposing it to the enzyme system involved in heme biosynthesis. In 1972 we brought about the first total synthesis of a specifically ^{14}C-labeled uroporphyrinogen III **8**[11]. Using hemolyzed duck blood, this product could be converted into heme in surprisingly high yield[12]. Rearrangements could be ruled out by a determination of the labeling positions in the radioactive hemin thus obtained (**1**, FeCl instead of Fe). Subsequently *Scott et al.*[13] were able to demonstrate that **8** is also the starting point for the microbial synthesis of vitamin B_{12}. It is therefore probable that all the natural cyclic tetrapyrroles known so far stem from uroporphyrinogen III, which thus proves to be a key biogenetic building block[3].

3. The Problem of "Pyrrole Inversion"

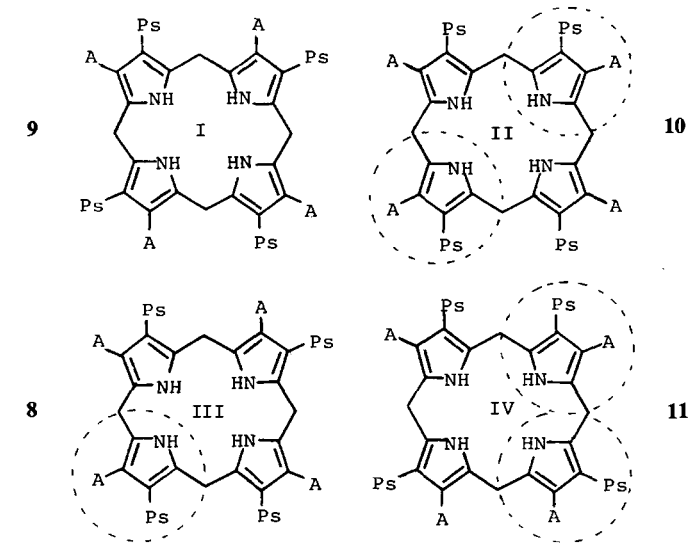
Many and sometimes contradictory hypotheses have been put forward in the last twenty years concerning the mechanism of the biosynthesis of uroporphyrinogen III **8** from porphobilinogen **7**, which includes the inversion of a pyrrole ring (in the dotted circle)[10]. The puzzling feature here was that only one pyrrole unit was inverted. However,



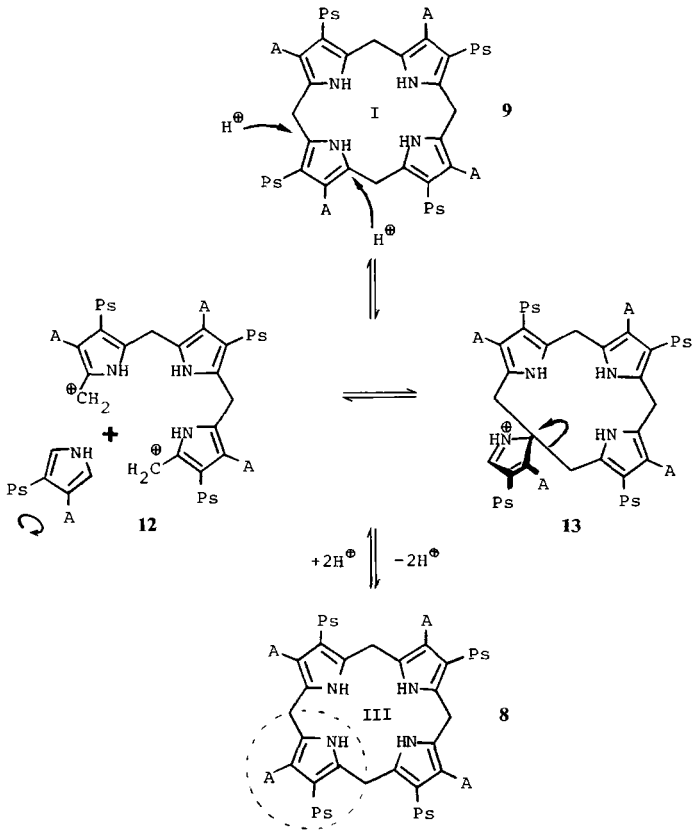
it is relatively easy to show that this is not nearly so remarkable as it first seemed.

In all there are four isomeric uroporphyrinogens (**8**–**11**), characterized by Roman numerals. In uroporphyrinogen I **9** all four pyrrole rings are arranged "in series", *i.e.* the acetic acid and the propionic acid side chains, denoted by "A" and "Ps" respectively, alternate regularly. In the heme precursor **8** one pyrrole ring is inverted (dotted circle). The remaining uroporphyrinogens II **10** and IV **11**, each with two inverted pyrrole rings, in contrast to isomers I and III have not yet been found in nature[8].

In their high reactivity the isomeric uroporphyrinogens resemble Mannich bases and are readily mutually interconverted under mild acid catalysis (Scheme 1). By protonation of the α-positions of the pyrrole rings the porphyrinogen system can be opened at one or more places. During

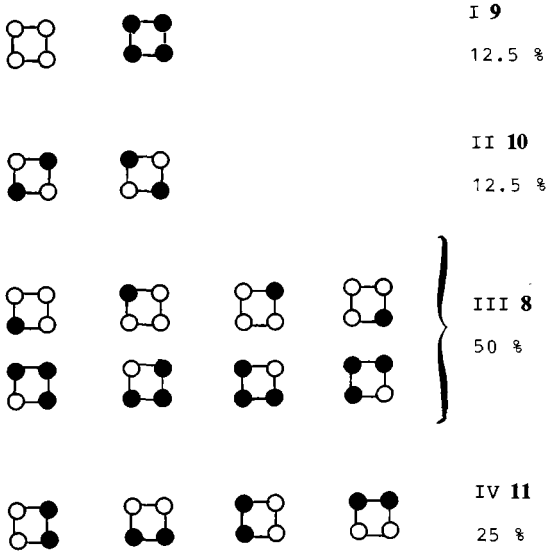


the proton-catalyzed intramolecular isomerization, inversion of all the pyrrole rings can occur *via* open-chain **12** or spirocyclic **13** intermediates[14].



Scheme 1. Proton-catalyzed isomerization of uroporphyrinogens exemplified by **9** and **8**.

Since the four isomeric uroporphyrinogens have practically identical stability, the composition of an equilibrium mixture is determined by the number of permutations that give rise to each isomer (Scheme 2)[15]. Of the 16 possible permutation products, eight are identical with uroporphyrinogen III **8** and only two with uroporphyrinogen I **9**. According to the permutation scheme an isomer ratio of 2:2:8:4 is expected for an equilibrium mixture of uroporphyrinogens I, II, III, and IV. *Mauzerall*[16] was first to be able to confirm this experimentally in the acid-catalyzed condensation of porphobilinogen **7**: uroporphyrinogen III **8** and/or its dehydrogenation product uroporphyrin III were the main products (50%).

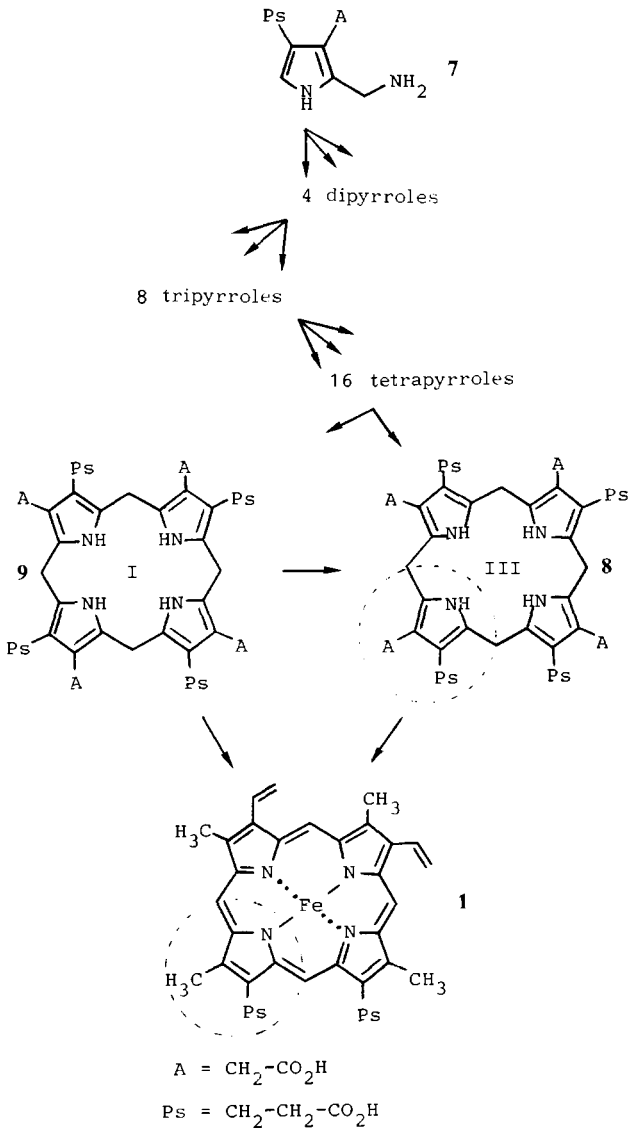


Scheme 2. The 16 possible permutations in the acid-catalyzed isomerization of uroporphyrinogens I—IV (**8**–**11**). Inverted pyrrole rings are shown as filled-in circles.

Considered in this light, the formation of uroporphyrinogen III **8** during the biosynthesis of heme is not puzzling[17–20]. The participant enzymes only increase the proportion of the reaction product that is considerably favored thermodynamically over its isomers. Similar phenomena are known in the biosynthesis of alkaloids[21,22].

The biosynthesis of the blood-pigment heme **1** from porphobilinogen **7** is summarized in simplified form in Scheme 3. Condensation of **7** leads *via* dipyrroles and tripyrroles to reactive tetrapyrroles, which are cyclized to uroporphyrinogens. Isomerizations with the inversion of one pyrrole unit can occur in each condensation step.

To check whether the pyrrole inversion occurs in somewhat preferred manner in certain parts of a kinetically controlled, enzymatic reaction sequence it would be necessary to isotopically label the rearranged and nonrearranged oligopyrroles (a total of 28 oligopyrroles) and then investigate their incorporation. This extensive and elaborate program has been partly realized by the efforts of several research groups[23–29]. To this end, isotopically labeled pairs of mono-, di-, and tripyrroles[25–29,45] and of uroporphyrinogens[30] have been synthesized in Münster. In each of these oligopyrrole pairs only one component contained an inverted pyrrole ring. In addition, the two components of each pair differed in that one was labeled with ^{14}C and the other with ^{3}H. By labeling with different isotopes it was possible to compare the incorporation of the components very reliably in one and the same experiment.



Scheme 3. Intermediates in the biosynthesis of heme **1** from porphobilinogen **7**.

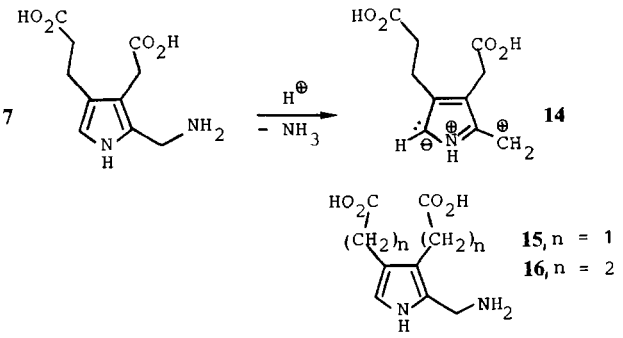
The biosynthesis experiments were carried out with the enzyme system from duck blood (*Shemin*[9]) on a scale which afterwards provided enough radioactive hemin — about 100 mg — for thorough purification to constant radioactivity. Without going into all the details of these extended chemical and enzymatic investigations some of the most important results will be mentioned. The ^{14}C- and ^{3}H-radioactivities of the hemin samples for both components of the pairs of isomers fed, revealed a significant although more or less differing incorporation into the blood pigment. This difference was especially conspicuous for the isomeric monopyrroles. In this case the incorporation rate for porphobilinogen **7** was 10—15 times higher than that of isoporphobilinogen (**7** with exchanged side chains "Ps" and "A"). As no chemical isomerization of the two monopyrroles was observed under the feeding conditions, the low incorporation of the isoporphobilinogen must be ascribed to some non-specificity of the enzyme system. A substantially higher non-specificity was observed in the incorporation of isomeric di- and tripyrroles.

Furthermore it is instructive that the incorporation rates of the monopyrroles and uroporphyrinogens are about 20 times higher than those of the highly reactive di- and tripyrroles. This gives rise to the assumption that the latter are especially strongly bound in the enzyme complex so that the labeled precursors supplied from outside can only be exchanged to a small extent. — In all these experiments the possibility of chemical condensation was critically taken into account.

Therefore, in the heme biosynthesis the condensation of porphobilinogen **7** *via* open-chain and cyclic oligopyrroles is accompanied by enzymatic isomerizations with inversion of individual pyrrole rings. The oligopyrroles are a kind of substrate pool for formation of the thermodynamically favored uroporphyrinogen III **8** and its further transformation into heme. These conclusions are applicable to biosynthetic experiments performed with fresh duck blood under *in vivo* conditions, which may more closely approach the situation prevailing in the organism than experiments with isolated enzymes. Recently, similar ideas on the participation of isomeric oligopyrrole precursors have also been suggested from experiments with isolated enzymes[31].

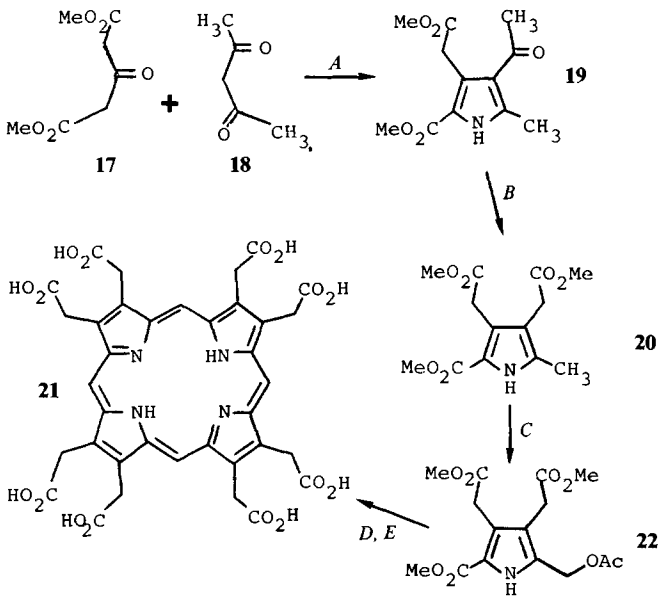
4. Biomimetic Syntheses

The question confronting the organic chemist is whether heme biosynthesis can serve as a pattern for the development of simple and effective porphyrin syntheses. In view of the central position of porphyrins in metabolism it would be highly desirable for biologically active porphyrins to be made more readily accessible than previously, *via* biomimetic syntheses of this kind. Thus, the uroporphyrinogen III **8** required for medico-diagnostic investigations currently still necessitates a 22-step total synthesis, and is marketed at the cost of $ 450 for 50 mg (*ca.* 500 times the price of gold). Among the reactions of heme biosynthesis, the cyclizing condensation of the monopyrrole porphobilinogen **7** is of particular significance for the development of biomimetic syntheses. **7** is a very reactive, bifunctional compound. On the one hand it can react with nucleophiles as a Mannich base at the aminomethyl group, and on the other has centers open to electrophilic attack at the α-positions of the activated pyrrole ring. Thus, under mild acid catalysis, intermolecular condensation with the release of ammonia can be expected *via* intermediate **14**, without the need for enzymes.



In fact, as *Cookson* and *Rimington*[32] had already established, under acid catalysis a mixture of isomeric uroporphyrins in which the biologically important isomer III **8** predominates is produced *in vitro* from **7** in high yield.

The formation of isomeric mixtures can be prevented if, in place of 7, similar pyrrole derivatives with two identical side chains at C-3 and C-4 are condensed. We therefore synthesized derivatives of the norporphobilinogen **15** and the homoporphobilinogen **16**[33], which under acid catalysis can be converted with good yields into homogeneous, readily crystallizing porphyrins[34]. A particularly simple and practical method is the synthesis of porphyrinoctaacetic acid **21** from the readily available acetonedicarboxylic acid ester **17** and acetylacetone **18**, a process which requires only a small number of steps (Scheme 4).



Scheme 4. Five-step synthesis of porphyrinoctaacetic acid **21**. *A:* Knorr condensation; *B:* $Tl(NO_3)_3$/MeOH; *C:* $Pb(OAc)_4$; *D:* Boiling in 20% HCl; *E:* Oxidation with O_2.

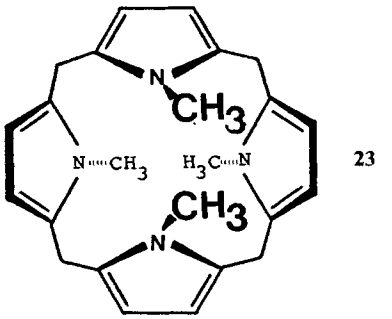
The porphyrinoctaacetic acid **21** differs from uroporphyrinogen III **8** only by the shortening of the four side chains by one C atom each. Because of the "natural" acetic acid side chains, also present in natural porphyrins, **21** is just as suited as **8** for many investigations of the chemical and physiological behavior. The same is true of the analogously synthesized porphyrinoctapropionic acid[34] (for further details see also **43** in Scheme 7).

Up to now octaethylporphyrin **24** was the porphyrin used most often as a model compound[35], but despite essential improvements in the syntheses[36-38] it does not satisfy the requirement for a more easily accessible and better water-soluble derivative[*].

It has also been possible to make use of the strong tendency of porphobilinogen **7** to cyclotetramerize in the biomimetic synthesis of unusual porphyrins[40], such as sterically strained porphyrinogens and porphyrins containing alkyl groups on the nitrogens, *e.g.* **23**.

[*] *J. B. Kim et al.* [39]: "*Dolphin et al.* [38] have recently developed an improved and reliable synthesis of octaethylporphyrin, but the reader is warned that even this synthesis is necessarily long and that in inexperienced hands the final product, rather than lustrous purple crystals, is often an intractable black polymer".

Since *N,N',N'',N'''*-tetraalkylporphyrinogens and porphyrins of this kind may be able to provide revealing information on the stereochemistry, aromaticity, spectroscopic properties, and structure-biological activity relationships of the porphyrin system, their synthesis was attempted by *Corwin* and *Quattlebaum* as early as 1936[41], and subsequently by several other groups. In their remarkable investigations, *Jackson, Johnson et al.*[42,43] succeeded in incorporating up to three *N*-methyl groups into the two chemically robust porphyrins **24** and **26** under vigorous experimental conditions (Scheme 5). Since *N,N',N'',N'''*-tetramethylporphyrins could not be obtained, it was assumed that these cannot exist because of the extreme strain on the methyl groups directed toward the center of the molecule.



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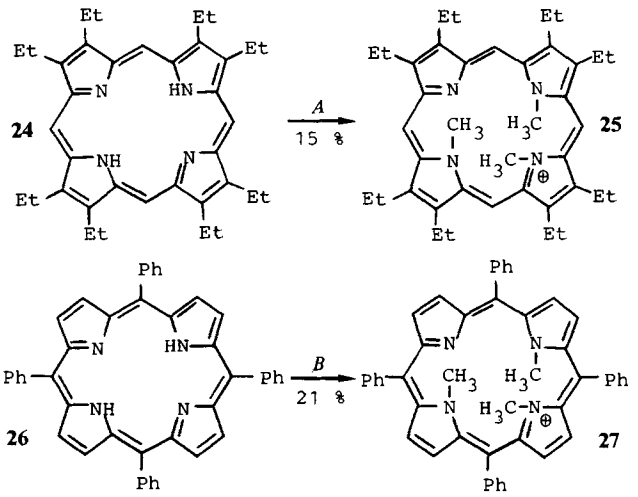
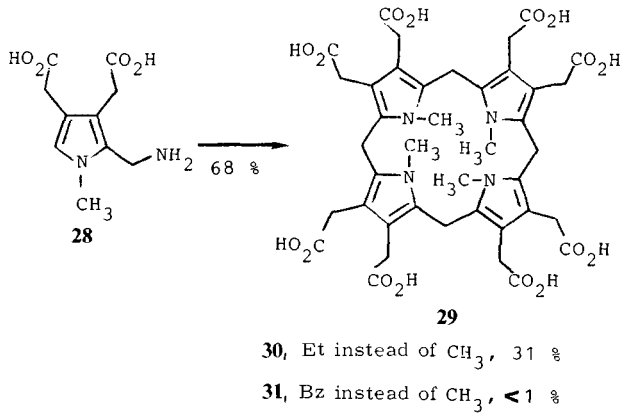


Scheme 5. *N*-Methylation of chemically robust porphyrins under vigorous conditions [42, 43]. *A:* CH_3SO_3F, 100°C, 120 h; *B:* CH_3I, $CHCl_3$, 60°C, 96 h.

Our attempts to prepare *N,N',N'',N'''*-tetramethylporphyrinogen **29** by a biomimetic synthesis exceeded all expectations. *N*-Methylnorporphobilinogen **28** served as the starting compound. After only 30 min of boiling in 0.5 N hydrochloric acid a product crystallized out in a high yield. After purification *via* the octamethyl ester, this product was found to be the desired compound **29** (Scheme 6). Encouraged by the practicability of the biomimetic principle, we were also able to obtain the tetraethyl and tetrabenzyl analogs **30** and **31** in the stated yields, which were lower as a result of increasing steric hindrance. According to model considerations, in porphyrinogens of this kind the pyrrole rings, including the *N*-alkyl groups, are rotated alternately "upward" or "downward" out of the porphyrin



Scheme 6. Biomimetic synthesis of **29**. 0.5 N HCl, 100 °C, 30 min. **30** and **31** can be obtained in analogous fashion.

plane. X-ray structure analysis[44] revealed that **29** in fact has a propeller-like structure (Fig. 2).

The non-planar structure of the *N,N',N'',N'''*-tetraalkylporphyrinogens is the reason for their unusual oxidation behavior. Whereas normal porphyrinogens are quickly dehydrogenated to dark-red aromatic porphyrins in the presence of atmospheric oxygen or iodine, the tetraalkyl derivatives remain unchanged under these conditions. Dehydrogenation is only possible with strong oxidizing agents such as cerium(IV) sulfate or bromine[45,36], whereupon green porphyrins such as **33** with two quaternary ammonium groups and interesting spectroscopic properties are obtained. Although, like the corresponding porphyrinogens, the *N,N',N'',N'''*-tetraalkylporphyrins cannot have a

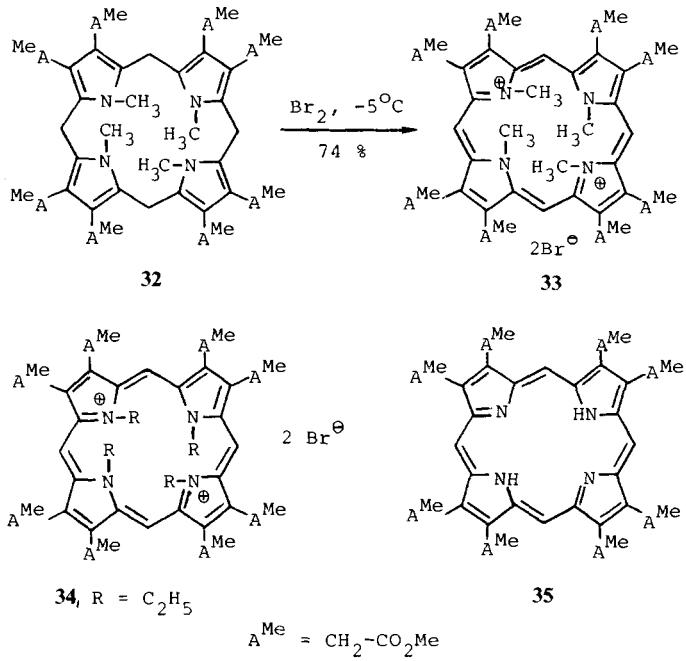


Table 1. ^{1}H-NMR-signals of *N,N',N'',N'''*-tetramethylporphyrinogen **32**, the bisquaternary *N,N',N'',N'''*-tetraalkylporphyrins **33** and **34** and the *N*-unsubstituted porphyrin **35** [46].

Compound	Solvent	^{1}H-NMR (δ values, TMS = 0) α- to δ-CH or CH_2	NH	N—CH_3
32	[D_6]acetone	3.80	—	2.60
33	CD_3CN	10.40	—	−4.31
34 [a]	CD_3CN	10.63	—	—
35	$CDCl_3$	9.98	−4.5	—

[a] N—CH_2 and N—CH_2—CH_3: $\delta = -5.35$ and -1.42, respectively.

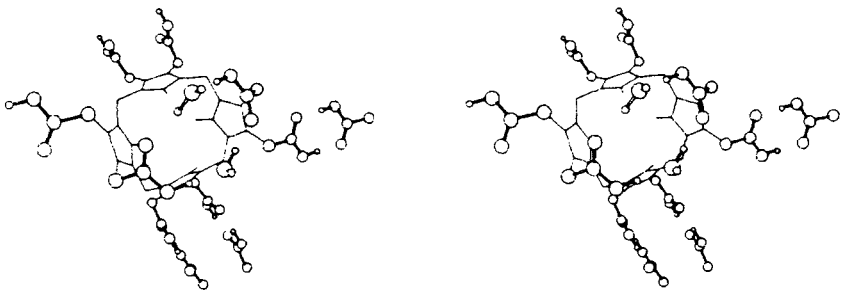


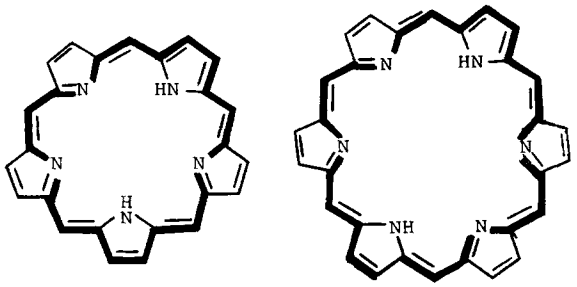
Fig. 2. Stereoscopic representation of *N,N',N'',N'''*-tetramethylporphyrinogen **29** in the crystal, after *Sawitzky* and *von Schnering* [44]. View almost along the C_2 axis. The porphyrinogen skeleton is shown as a line drawing, while the atoms of side chains bridging hydrate molecules are represented by circles.

planar structure because of steric interaction of the *N*-alkyl groups, the aromatic character of their 18π-electron system is apparently hardly impaired. This can be seen very clearly from a comparison of the ring-current influenced ^{1}H-NMR signals of the bisquaternary *N,N',N'',N'''*-tetraalkylporphyrins **33** and **34** with those of the *N*-unsubstituted, planar porphyrin **35** and the *N,N',N'',N'''*-tetramethylporphyrinogen **32** (Table 1).

5. Extreme Selectivity of Porphyrin Formation

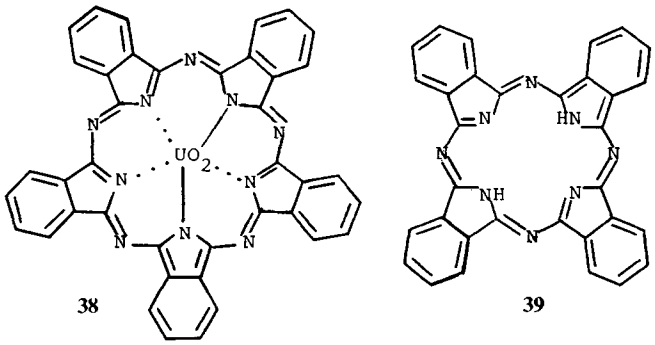
The biomimetic cyclotetramerization of the monopyrrole porphobilinogen **7** and its derivatives deserves closer consideration. Thus, careful chromatographic analyses revealed only the formation of porphyrins and hardly any by-products. In the condensation of a bifunctional compound of type **7**, in addition to the cyclic tetrapyrroles one would normally expect to find open-chain oligopyrroles and higher cyclic oligomers, such as cyclic pentapyrroles or hexapyrroles. The higher cyclic oligopyrroles could, like the porphyrins, all have aromatic, ring-conjugated annulene structures; the hypothetical [22]- and [26]annulenes **36** and **37** are examples.

Whereas porphyrins with more than five pyrrole rings are still unknown, *Day et al.*[47] succeeded in synthesizing a phthalocyanine of this kind, **38**, which because of its remarkable properties was called "superphthalocyanine". Its synthesis from phthalodinitrile was carried out using the



36 37

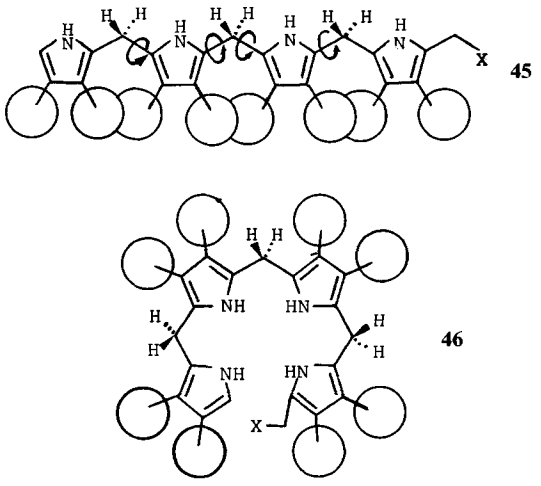
large uranyl cation as a complexing matrix. The dark-green superphthalocyanine is characterized by the fact that its longest-wavelength absorption maximum is displaced into the near infrared (953 nm) relative to the normal phthalocyanine complexes. Under the influence of trifluoroacetic acid at room temperature[48] or of $CuCl_2$[49], **38** decomposes into phthalodinitrile and phthalocyanine **39** or its copper complex. The formation of the cyclic tetramer is accordingly also strongly preferred in the phthalocyanines.



38 39

To acquaint ourselves with the selectivity of the formation of porphyrins and with the degree of instability of the higher cyclic oligopyrroles ("superporphyrins"), we carried out directed syntheses[50-52] based on the aldol-like condensation of the dialdehyde **40** with linear oligopyrroles (Scheme 7).

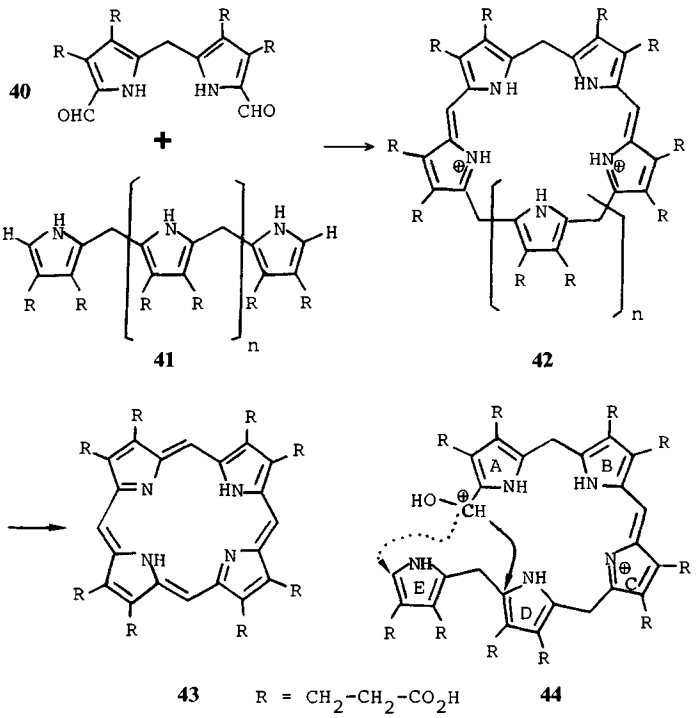
This reaction leads to cyclic oligopyrroles **42** with two pyrromethene structures which stabilize the ring system against further dehydrogenation. The propionic acid side chains also present in natural porphyrins were selected for the protection of the β-positions of the pyrrole rings and because of their favorable solubility characteristics. The four linear oligopyrroles **41a—41d** were synthesized by a simplified method that avoids the conventional use of ester protecting groups at the α-positions of the pyrrole rings[51]. Coupling the dialdehyde **40** with linear dipyrroles, tripyrroles, tetrapyrroles, and pentapyrroles **41a—41d**, as a result of which pyrrole-homologous porphyrins with respectively four, five, six, and seven pyrrole rings had been expected, gave a surprising result: under the very mild conditions used (0.25% hydriodic acid in glacial acetic acid at room temperature) only one cyclic tetrapyrrole was formed in each case, and this was oxidized to the porphyrin **43**[52]. This is conclusive proof of the very strong preference for porphyrins compared to other condensation products. An explanation of this preference can be derived by considering the possible conformations of open-chain tetrapyrrole porphyrin precursors (Fig. 3)[29,52].



45 46

Fig. 3. Linear **45** and helical conformations **46** of an open-chain porphyrin precursor [29]. X = electronegative leaving group.

In the linear conformation **45** there is a strongly destabilizing steric interaction of the side chains in the β-position. In the helical conformation **46**, which differs from the linear by rotation around single bonds (shown by circular arrows), only a small interaction of this kind is found; this conformation provides the optimal prerequisites for ring closure to afford porphyrins. Although other conformations between the extremes represented by **45** and **46** can be envisaged, such considerations reveal a steric preference for the porphyrin-forming helical conformation **46**. This makes it possible to derive the mechanism of preferred porphyrin formation illustrated by **44** in the reaction of **40** with linear oligopyrroles **41a—41d** (Scheme



43 R = CH_2-CH_2-CO_2H 44

Scheme 7. Course of the reaction of dialdehyde **40** with linear oligopyrroles **41a—41d**. **a, b, c, d:** n = 0, 1, 2, 3.

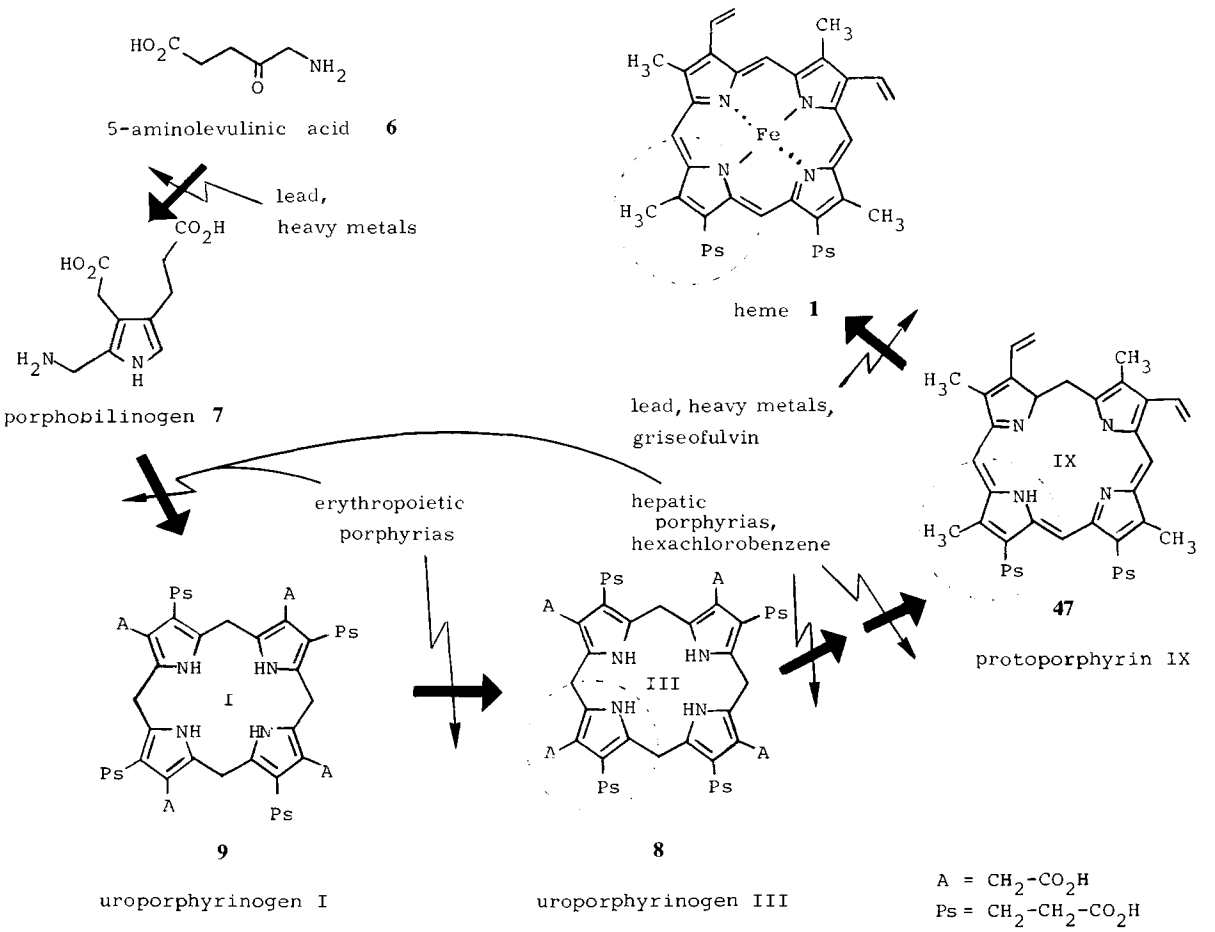
7). For example, if **40** reacts with **41b** in an acid medium, a linear pentapyrrole **44** with a protonated aldehyde group is formed first. As the arrows show, there are two possibilities for electrophilic attack of the carbocation at the electron-rich α-positions of the adjacent pyrrole rings. Because of the cyclic conformation of **44**, attack at the fourth pyrrole ring D is favored over that at the fifth pyrrole ring E. The product thus formed then stabilizes itself by elimination of one pyrrolylmethyl cation, to furnish the cyclic tetrapyrrole (porphyrin) **43**.

In these investigations, as in biomimetic syntheses, the porphyrins proved to be the products of an extremely selective and thermodynamically-favored cyclization proceeding in high yields, even in the absence of enzymes. It is therefore not surprising that porphyrins are also found among the reaction products of a simulated "primeval atmosphere"[53-55]. Porphyrins can thus be included among the prebiotic compounds, *i. e.* those that were already present before the emergence of life on Earth. In the evolution of organisms they proved to be advantageous ligands for catalytically-active heavy-metal ions in enzymes, and were also particularly advantageous because the favored formation of porphyrins is relatively insensitive to enzymatic interference.

6. Explanation of the Metabolic Disease Porphyria

The biosynthesis of the red blood pigment is a central metabolic process whose normal operation is regulated by many enzymes, and an inhibition of individual enzymes as a result of endogenous or exogenous influences gives rise to serious disorders (Scheme 8). Thus, lead poisoning is accompanied by inhibition of δ-aminolevulinic acid dehydratase, the enzyme responsible for the condensation of 5-aminolevulinic acid **6** to porphobilinogen **7**. Lead poisoning is recognized, among other effects by an increased concentration of **6** in the urine. When enzymes from later stages of the heme biosynthesis are inhibited, porphyrins that cannot be converted accumulate further and the urine assumes a reddish color. Metabolic disorders of this kind are known as porphyrias[5-7]. In the comparatively rare, congenital erythropoietic porphyrias the inhibition mainly affects the enzymes causing the production of uroporphyrinogen I **9** and its conversion into uroporphyrinogen III **8**. In hepatic porphyrias the inhibition affects decarboxylases which in heme biosynthesis convert the uroporphyrinogen III **8** into protoporphyrin IX **47** *via* coproporphyrinogen III. Porphyrias can also be triggered by a variety of metabolic toxins and by drugs. In one critical clinical evaluation this was found to be the case for more than 100 drugs, including barbiturates, sulfonal, ergot alkaloids, griseofulvin, estrogen, and also ethanol[55].

The porphyrins produced in porphyrias, which cannot be converted into heme, accumulate in all organs of the



Scheme 8. Inhibition of heme biosynthesis in porphyrias and under the influence of toxins (after [5]).

body. Among other symptoms, this is recognizable by deep-red staining of the tooth roots and the teeth themselves. The severe damage that light can inflict upon affected persons is characteristic. Because of the photosensitizing action of uroporphyrin excreted in the skin, the patient suffers from blisters which are easily infected and leave scars. This can ultimately result in leprosy-like damage to facial skin and in mutilation of the extremities *e.g.* the fingers (Fig. 4).

Fig. 4. Skin and tissue damage in a porphyria patient (from [65]).

In pathophysiological studies on porphyrias it is noted that the biochemical mechanism of the action of light on skin sensitized by porphyrins has not yet been clarified[56,57]. It seemed to us important to help toward the resolution of this medical problem by model chemical investigations. In particular we wanted to consider the possibility—hitherto hardly considered—of the involvement of singlet oxygen. As a result of the biomimetic syntheses[33,34] and labeling experiments[11,27,30], physiologically relevant porphyrins were available for us in adequate supply. We asked ourselves three questions about photodermatosis in porphyrias:

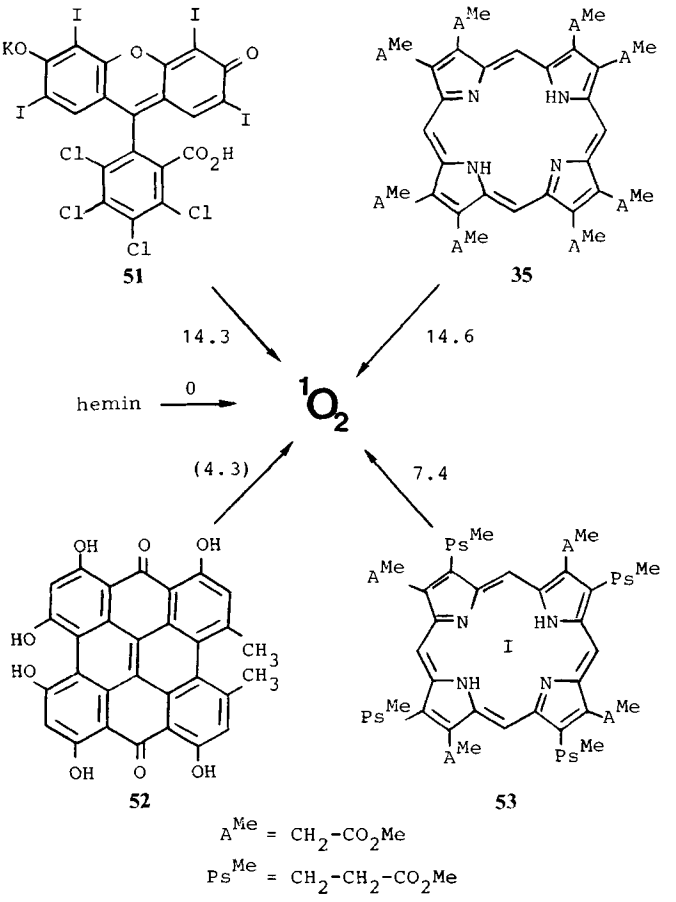
1) How suitable are porphyrin intermediates in heme biosynthesis as sensitizers for the formation of singlet oxygen?

2) Do such porphyrins accelerate the photochemical degradation of vitamin A?

3) What are the structure and the biological activity of products of the reaction between vitamin A and singlet oxygen?

Re 1: The formation of singlet oxygen by porphyrins and other photodynamically active natural products should be compared as quantitatively as possible with that of known photosensitizers under standardized conditions.

Cycloaddition of $^1O_2$ with 2,5-dimethylfuran **48**[58] is suitable for this purpose, since it permits the singlet oxygen to be captured and determined as a crystalline, solvolyzed adduct **50**. Some of the results are summarized in Scheme 9[60] Uroporphyrin I **9**, which is deposited in the tissue in porphyrias in the form of its octamethyl ester **53** is almost as good a generator of singlet oxygen as bengal rose **51**. The same is true of the porphyrin **35** produced by biomimetic synthesis[34]. As expected, hemin did not form any singlet oxygen.

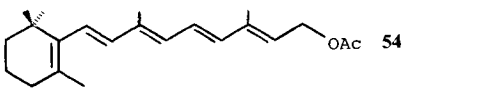


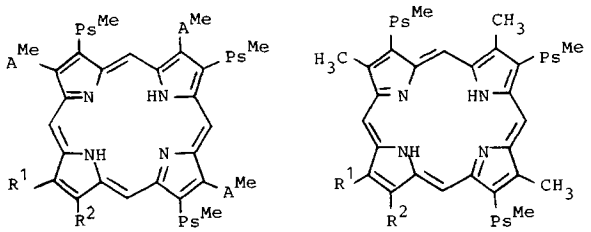
Scheme 9. Comparison of formation of singlet oxygen (in mmol) by hemin and by the four photosensitizers **35**, **51**, **52**, and **53** under standardized conditions (5 μmol of the sensitizer in methanol, 20 min irradiation). Hypericin **52** yielded the value given in parentheses only when used in 10 times higher concentration at double the irradiation time [60].

The behavior of hypericin **52** is remarkable. As a photodynamically active substance from the common hypericum (St. John's wort) *Hypericum perfovatum*, it causes the dermatoses known as hypericism in grazing cattle[59]. In sunny regions these dermatoses are so serious that in addition to total eradication of the plant, which is not without its problems, pasturing by night and staining the cattle a dark

color as a protection against sun light are actually practiced[59]. The ability of **52** to form singlet oxygen is, however, much smaller than that of the porphyrins and only becomes noticeable after a considerable increase of its concentration and prolongation of the illumination period (Scheme 9). The porphyrins deposited in a pathological disturbance of heme biosynthesis are therefore more dangerous than hypericin **52**, which has long been known as a photodynamically active substance.

Re 2: We investigated to what extent physiologically important porphyrins accelerate the photochemical conversion of the epithelium-preserving vitamin A *via* the production of singlet oxygen[60]. Again using standardized conditions, we studied how long it takes 60 mg of vitamin A acetate **54**—nearly an adult's monthly requirement—to be photochemically degraded or converted to half and to one-tenth of the initial quantity in the presence of various sensitizers (Table 2). It should be particularly noted that on illumination, very small quantities (1 μmol) of the porphyrins tested, corresponding to about only 1/1000 of the quantity occurring in porphyria patients, were sufficient to destroy a month's supply of vitamin A within minutes.





53, R^1 = Ps^{Me}, R^2 = A^{Me} **56**, R^1 = Ps^{Me}, R^2 = CH_3

55, R^1 = A^{Me}, R^2 = Ps^{Me} **57**, R^1 = CH_3, R^2 = Ps^{Me}

A^{Me} = CH_2-CO_2Me; Ps^{Me} = CH_2-CH_2-CO_2Me

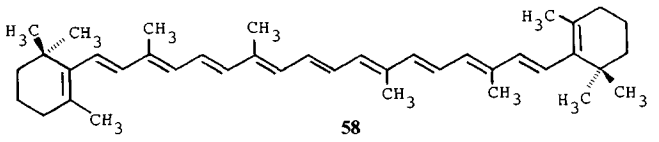
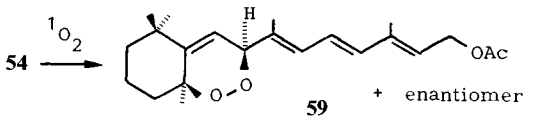


Table 2. Conversion of vitamin A acetate **54** by singlet oxygen under standard conditions (60 mg of **54**, 1 μmol of sensitizer). The times given are those after which the amount of **54** falls to 50% ($t_{1/2}$) and to 10% ($t_{10\%}$) of the original amount [60].

Sensitizer	$t_{1/2}$ [min]	$t_{10\%}$ [min]
Bengal rose **51**		12
Uroporphyrin-I-octamethyl ester **53**	13	41
Uroporphyrin-III-octamethyl ester **55**	9	25
Coproporphyrin-I-octamethyl ester **56**	8	23
Coproporphyrin-III-octamethyl ester **57**	7	22
Blank experiment	36	
53 + β-Carotene **58**	> 50	

The formation of singlet oxygen and thereby the destruction of vitamin A acetate **54** was thought to be preventable by the addition of a singlet oxygen quencher[61] such as β-carotene **58**. This indeed proved to be the case (Table 2). This result provides a mechanistic explanation of the clinical use of **54** in doses of 50 to 100 mg per day in the treatment of photodermatosis in porphyrias[62,63]. Our experiments permit the conclusion that, on exposure to light, the porphyrins deposited in skin in porphyrias form singlet oxygen, whose reaction with vitamin A gives rise to a local avitaminosis, destroying the epithelium.

Re 3: We isolated the endoperoxide **59** in 60% yield as the main product of the conversion of vitamin A acetate **54** induced by pathological porphyrins as $^1O_2$ generators (see Table 2). The structure of this peroxide corresponds to that of analogous endoperoxides obtained from vitamin A derivatives by photosensitization with bengal rose **51**[64]. The endoperoxide **59** obtained from vitamin A acetate has no Vitamin A activity in the chicken test and is non-toxic when administered orally to mice[60].



7. Outlook

The porphyrin skeleton in the red pigment of blood is one of the oldest organic molecules on Earth, probably older than life itself. Model experiments with simulated primeval atmospheres[53,54] suggest that porphyrins arose even in the prebiotic era. Their formation was later enzymatically optimized when living organisms made use of them to complex catalytically active metal ions. The biosynthesis of heme and the porphyrins has since become a principal strand in the metabolic network of organisms. It may be likened to a silk thread on which our life hangs, increasingly endangered by forces of heredity and the effects of civilization. Thus medicine imposes important future tasks on the organic chemist in the field of porphyrins, an area which is just beginning to become accessible by simple biomimetic syntheses.

I am indebted to all my coworkers mentioned in the cited studies for their creative and stimulating collaboration in the broadly-based study of heme biosynthesis. I am also grateful to colleagues in the field all over the world who led us to undertake intensive work in this field—not really so complicated as it sometimes seems—both by enlightening and puzzling contributions. The work has been generously and patiently supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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N-(Pentafluoro-λ^6-sulfanyl)iminosulfur Tetrafluoride by Reaction of Thiazyl Trifluoride with Fluorine**

By *Alfred Waterfeld* and *Rüdiger Mews**

Reaction of NSF_3 and fluorine at room temperature yields SF_6 and N_2:

$$\underset{\mathbf{1}}{NSF_3} + 3/2\,F_2 \rightarrow SF_6 + 1/2\,N_2 \qquad (1)$$

No products containing nitrogen-fluorine bonds are formed, and therefore the reaction could be used for the fluoro-calorimetric determination of the enthalpy of formation of **1**[1].

We have now found that even under controlled, mild reaction conditions no [2] products with N—F bonds are formed, but instead the title compound **2**, SF_6, and N_2:

$$\mathbf{1}_{exc} + F_2 \xrightarrow{-196 \rightarrow -78 \rightarrow 20\,^\circ C} \underset{\mathbf{2}}{F_5SNSF_4} + SF_6 + N_2 \qquad (2)$$

Reaction commences at about $-78\,^\circ C$, recognized by a slow drop in pressure (the number of molecules decreases).

A drastic change in the experimental conditions, *e.g.* rapid heating or addition of BF_3 or HgF_2, leads to explosive-like reaction; SF_4 and N_2 are formed.

Reaction (3) is strongly exothermic (-415.9 kJ/mol):

$$\mathbf{1} + 1/2\,F_2 \rightarrow \{NSF_4^{\oplus}\} \rightarrow SF_4 + 1/2\,N_2 \qquad (3)$$

Thus, **2** is formed only under kinetic control in liquid **1** at temperatures slightly above $-78\,^\circ C$. The yield of **2** (maximum 50% referred to reacted fluorine) is higher, the smaller the ratio F_2 : **1**.

We assume that **1** is oxidized by fluorine radicals *via* short-lived intermediates to the radical $SF_5^{\oplus}$, which not only reacts with F_2 to give SF_6, but also with the solvent **1** to give $F_5SNSF_3^{\oplus}$. The latter stabilizes with formation of **2** and a fluorine radical, which continues the chain reaction:

$$\underset{\mathbf{1}}{SF_5^{\oplus} + NSF_3} \rightarrow \{F_5SNSF_3^{\oplus}\} \rightarrow \underset{\mathbf{2}}{F_5SNSF_4} + F^{\oplus} \qquad (4)$$

2 is a stable, colorless liquid (b.p. $49\,^\circ C$, m.p. $< -100\,^\circ C$) at room temperature, and can be heated to $60\,^\circ C$ in metal or Kel-F vessels, but decomposes in glass—particularly in the presence of traces of moisture—to F_5SNSOF_2[3].

The IR spectrum of **2** (gas) shows, aside from ν(SN) at 1299 cm^{-1} (s), strong bands at 922 (vs), 841 (s), and 794 cm^{-1} (s), which can be assigned to the stretching vibrations of the SF_5- and SF_4-groups. The ^{19}F-NMR spectrum at $0\,^\circ C$ is of AB_4X_4 type ($\delta_A = 70.4$, $\delta_B = 78.1$); the NSF_4 group gives a broad singlet ($\delta = 77.75$)[4]. On lowering the temperature, a further broadening occurs; at $-70\,^\circ C$ only the AB_4 part for the SF_5-group is observed ($\delta_A = 70.65$, $\delta_{B_4} = 77.96$, $J_{AB} = 155.6$ Hz).

The NSF_4 group in **2** can function both as fluoride donor and as fluoride acceptor:

$$\mathbf{2} + AsF_5 \xrightarrow[-50 \rightarrow -20\,^\circ C]{SO_2ClF} \underset{\mathbf{3},\ \text{m.p. } 103\,^\circ C}{F_5SNSF_3^{\oplus}AsF_6^{\ominus}} \qquad (5)$$

$$\mathbf{2} + CsF \xrightarrow[14\,d]{20\,^\circ C} \underset{\mathbf{4}}{Cs^{\oplus}[N(SF_5)_2]^{\ominus}} \qquad (6)$$

The salt like structure of **3** follows from the ^{19}F-NMR spectrum.

The IR spectroscopically characterized salt **4**, whose anion contains two geminal pentafluoro-λ^6-sulfanyl groups, opens up an entry to bis(pentafluoro-λ^6-sulfanyl)amides[9].

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$$\mathbf{1} + 2\,HF \rightarrow F_5SNH_2 \xrightarrow{2F_2} F_5SNF_2 + 2\,HF$$

(A. Waterfeld, R. Mews, unpublished work).

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Bis(pentafluoro-λ^6-sulfanyl)amines**

By *Alfred Waterfeld, Heinz Oberhammer*, and Rüdiger Mews**

$F_2C(SF_5)_2$[1] and F_5SOSF_5[2,3] are the only compounds with two geminal pentafluoro-λ^6-sulfanyl groups to have been reported in the literature so far. The *N*-(pentafluoro-λ^6-sulfanyl)iminosulfur tetrafluoride **1** prepared by us[4] now opens up access to bis(pentafluoro-λ^6-sulfanyl)amines. Thus, addition of hydrogen fluoride to **1** affords $(SF_5)_2NH$ **2** in quantitative yields:

$$\underset{\mathbf{1}}{F_5SNSF_4} + HF \rightarrow \underset{\mathbf{2}}{(SF_5)_2NH} \quad (1)$$

The colorless liquid **2**, b.p. 60.4 °C, is stable at room temperature in glass; at elevated temperature in presence of alkali-metal fluorides, it loses HF with re-formation of **1**. **2** is a weak acid; with large cations, salts such as $Ph_4P^{\oplus}N(SF_5)_2^{\ominus}$ **3** can be precipitated.

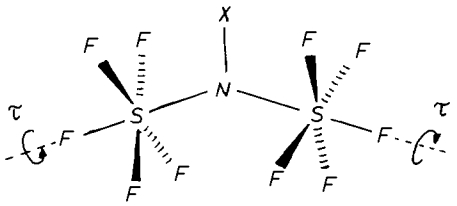
The *N*-halobis(pentafluoro-λ^6-sulfanyl)amines **5** and **6** are accessible in 91 and 87% yield, respectively, *via* the cesium salt **4**[4]:

$$\underset{\mathbf{4}}{Cs^{\oplus}N(SF_5)_2^{\ominus}} + F_2 \rightarrow \underset{\mathbf{5}}{FN(SF_5)_2} + CsF \quad (3)$$

$$\mathbf{4} + ClF \rightarrow \underset{\mathbf{6}}{ClN(SF_5)_2} + CsF \quad (4)$$

5 and **6**, b.p. 51.6 and 78 °C, respectively, are stable, colorless liquids at room temperature. Owing to the polarity of the Cl—N bond, **6** is considerably more reactive than **5**; **6** is rapidly decomposed by halide ions (Cl^-, Br^-). Since the two SF_5 groups couple with each other, the NMR spectra of the bis(pentafluoro-λ^6-sulfanyl)amines are quite complicated ($AA'B_4B_4'$ or $AA'B_4B_4'X$ spectra).

The structures of **2** and **5** were determined by electron diffraction.



2, X = H; **5**, X = F

2 and **5** have planar S_2NX frameworks with large SNS angles (134.8 ± 1° and 138.3 ± 1.0°, resp.). The SN distances increase with increasing electronegativity of the substituents, *e.g.* **2** < **5** < F_5SNF_2[5], but in all cases are shorter than the Schomaker-Stevenson value (1.74 Å). The average SF distances show an opposite trend.

The two latter mentioned findings can be qualitatively explained by a simple electrostatic model.

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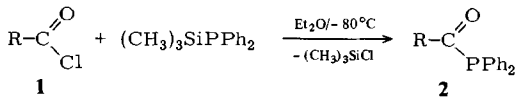
(Chloroacyl)diphenylphosphanes as Sources of Halogenated Ketenes**

By *Ekkehard Lindner*, Michael Steinwand, and Sigurd Hoehne*

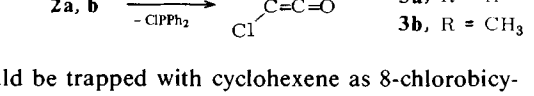
Because of their polar cumulative double-bond system, chloroketenes are highly reactive compounds, which add to olefins, and thus are of special preparative interest[4]. We have now succeeded[7] in isolating and characterizing the pure chloroketones **3a** and **3b**, hitherto unknown in substance. Thermolysis of the (chloroacyl)diphenylphosphanes **2a** and **2b**, which were synthesized for the first time by reaction of $(CH_3)_3SiPPh_2$ with the acyl halides **1**, afforded **3a** and **3b**, which were isolated and characterized by freezing out at −80 °C, and by ^{13}C-NMR spectroscopic measurements at −60 °C.



1 **2**

a, R = $HCCl_2$; **b**, R = CH_3CCl_2; **c**, R = CCl_3

The crystalline acylphosphanes **2a—2c**, which are readily soluble even in slightly polar solvents, were identified by elemental analyses and by their ^{13}C-, $^{31}P\{^1H\}$-NMR, IR, and mass spectra; in the case of **2a**, also by an X-ray structure analysis (Fig. 1). **2a—2c** are thermally labile and decompose even under mild conditions into $ClPPh_2$ and ketene derivative.



3a, R = H
3b, R = CH_3

3a could be trapped with cyclohexene as 8-chlorobicyclo[4.2.0]octan-7-one. Various products are formed on decomposition of **2c**, depending on the temperature: Between 0 and 40 °C, Cl_3PPh_2 is formed; on briefly heating to 80 °C, $ClPPh_2$ can be observed $^{31}P\{^1H\}$-NMR spectroscopically and is found to be further chlorinated to Cl_3PPh_2 after a short while. This would suggest that dichloroketene occurs as intermediate. The signals of the Cl atoms in the ^{13}C-NMR spectra of **3a** and **3b** are shifted upfield compared to the corresponding signals of ketene and methylketene[11] [$^{13}C\{^1H\}$-NMR ($CDCl_3$) **3a**: $\delta = 166.2$; **3b**: $\delta = 168.9$]; consistent with this finding the C2 atoms in **3a** and **3b** are less shielded [^{13}C-NMR ($CDCl_3$) **3a**: $\delta = 70.1$ (d, $^1J_{CH} = 184.4$ Hz); **3b**: $\delta = 85.0$ (q, $^2J_{CH} = 4.5$ Hz)].

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

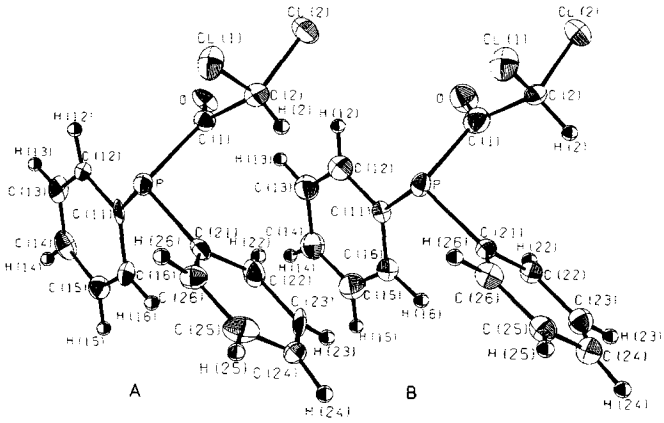

Fig. 1. ORTEP diagram of the structure of **2a** in the crystal.

The crystal lattice[12] of **2a** accomodates two sets of mutually symmetry-independent molecules (A, B). In accord with the $^{31}P\{^1H\}$-NMR spectrum, the X-ray structure analysis of **2a** also indicates an interaction between Cl1 and the lone pair of the phosphorus, which favors the thermal decomposition (Cl1—P distance = 327 pm). The PCl bond, of *ca.* 188 pm, is longer than the PC_{alkyl} bonds; this is important, since cleavage of this bond is an important prerequisite for the formation of **3a**.

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CAS Registry numbers:
1a, 79-36-7; **1b**, 26073-26-7; **1c**, 76-02-8; **2a**, 81456-78-2; **2b**, 81456-79-3; **2c**, 81456-80-6; **3a**, 29804-89-5; **3b**, 13363-86-5; **4**, 81456-81-7; cyclohexene, 110-83-8; $(CH_3)_3SiPPh_2$; 17154-34-6.

[4] W. T. Brady, *Tetrahedron 37* (1981) 2949.
[7] E. Lindner, H. Lesiecki, *Z. Naturforsch. B 33* (1978) 849.
[11] J. Firl, W. Runge, *Z. Naturforsch. B 29* (1974) 393; *Angew. Chem. 85* (1973) 671; *Angew. Chem. Int. Ed. Engl. 12* (1973) 668.
[12] **2a** crystallizes from ether monoclinically; space group $P2_1/c$, $a = 1113.4(6)$, $b = 1345.6(3)$, $c = 1811.0(5)$ pm, $\beta = 96.76(3)°$, $Z = 8$, $\rho_{calc} = 1.465$ g cm^{-3}. Diffractometer measurements at -110 °C. The structure was refined anisotropically to $R = 0.034$ (apart from H) using direct methods and Difference-Fourier syntheses for 2157 independent reflections ($\theta = 3–23°$) with the SHEL-76 program system.

Light-Induced Activation of 7-Dehydrocholesterol

By *Karlheinz Schmitt-Rau** and *Manfred Wilk*

It has long been presumed that autoxidation products of cholesterol and its derivatives participate in carcinogenesis[1]. We have been able to show[5] that 7-dehydrocholesterol (7-DHC) and ergosterol can be oxidized to reactive alkylating species which could possibly react as precarcinogens with cell nucleophiles. 7-DHC is present as provitamin D_3 in high concentrations in the skin. Should it likewise be activated in this way by irradiation such that it reacts with a model nucleophile—1-methylimidazole—this could give an indication of the mechanism of light-induced carcinogenesis.

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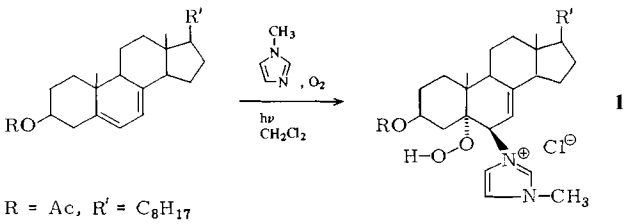
After 120 hours irradiation of the acetate of 7-DHC (or of 7-DHC itself) and 1-methylimidazole in dichloromethane, a 1 : 1 adduct of the steroid and nucleophile could be isolated following the purification steps described in [5]. Elemental analysis revealed the presence of two additional oxygen atoms in the molecule. The adduct reacts—on a thin-layer chromatographic plate—with *N,N,N',N'*-tetramethyl-*p*-phenylenediamine, giving a blue coloration indicative of formation of a hydroperoxide. On subsequent treatment with a saturated aqueous solution of Na_2SO_3 the hydroperoxy group is reduced to a hydroxy group. The cisoid-conjugated double bond system of 7-DHC is no longer present in the product, as indicated by the absence of a band at 270–280 nm in the UV spectrum. The adduct was ^{1}H-NMR spectroscopically identical with the product of the Fenton reaction of 7-DHC[5]. According to all the above data the adduct formed in the photoreaction has the structure **1**. The ^{13}C-NMR spectrum is also consistent with this proposed structure[7].



1

R = Ac, R' = C_8H_{17}

Photoactivated 7-DHC is thus indeed capable of alkylating nucleophiles such as 1-methylimidazole. *Black et al.*[13] found that 5α,6α-epoxycholesterol, a well-known carcinogen, is formed on UV irradiation of skin preparations. It appears plausible that irradiation of 7-DHC *in vivo* leads to similar metabolites, which can be effective as "ultimate carcinogens". Hence, the reaction described here can be considered as a model reaction for the initiation of light-induced cancer illnesses.

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CAS Registry numbers:
1, 81456-85-1; 7-DHC 3β-acetate, 1059-86-5; 1-methylimidazole, 616-47-7.

[1] G. O. Schenck, K. Gollnick, O. A. Neumüller, *Justus Liebigs Ann. Chem. 603* (1957) 46.
[5] M. Wilk, K. Schmitt, *Z. Naturforsch. B 36* (1981) 248.
[6] L. L. Smith, F. D. Hill, *J. Chromatogr. 66* (1972) 101.
[7] M. Wilk, K. Schmitt, *Org. Magn. Reson. 15* (1981) 329.
[13] H. S. Black, W. B. Lo, *Nature 234* (1971) 306.

Unsymmetrical Transfer of Allyl Groups in the Reaction of $[(\eta^3\text{-}C_3H_5)_2M]$ (M = Pd, Ni) with Bis(diphenylphosphino)maleic Anhydride**

By *Dieter Fenske** and *Petra Stock*

Phosphino derivatives of maleic anhydride are able to form complexes with transition metals in which the metal has formally more than 18 valence electrons[1,3]. Compounds of this type have a tendency to undergo subse-

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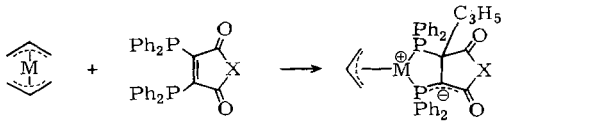
quent reactions[4–6]. We now report the reaction of the bis(η^3-allyl) complexes of Pd and Ni, **1** and **2**, respectively, with bis(diphenylphosphino)maleic anhydride and bis(diphenylphosphino)-*N*-methylmaleimide. **1** and **2** react with the maleic acid derivatives *via* transfer of a π bonded C_3H_5 group to afford the diamagnetic compounds **3** and **4**, respectively.



1, M = Pd X = O, NCH_3 **3**, M = Pd, X = O
2, M = Ni **4**, M = Ni, X = NCH_3

A short-lived intermediate free radical, which from the hyperfine structure and coupling constants must be a maleic acid derivative, can be detected in this reaction by ESR spectroscopy. An X-ray structure analysis of **3** (Fig. 1) indicates that Pd is bonded to two PPh_2 groups and to a C_3H_5 group in a *trihapto* fashion. Because of the allyl

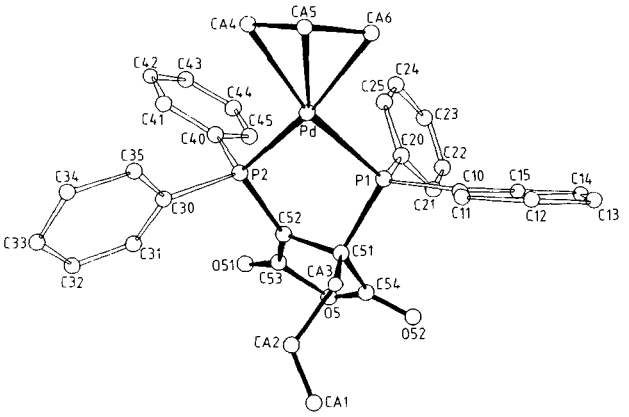


Fig. 1. Molecular structure of **3** in the crystal.

group on C51, the complex is chiral. Both electrons of the double bond in the free maleic acid derivative are formally localized on C52 in the complex; the charge of the carbanion thus formed is compensated by Pd^{1+}.

Spectroscopic data (^{31}P-NMR: $\delta = -19.2$ and -66.0; IR (KBr): ν(CO) = 1756 and 1705 cm^{-1}) and bond lengths, however, suggest delocalization of the lone pair of electrons into the neighboring CO and PPh_2 groups.

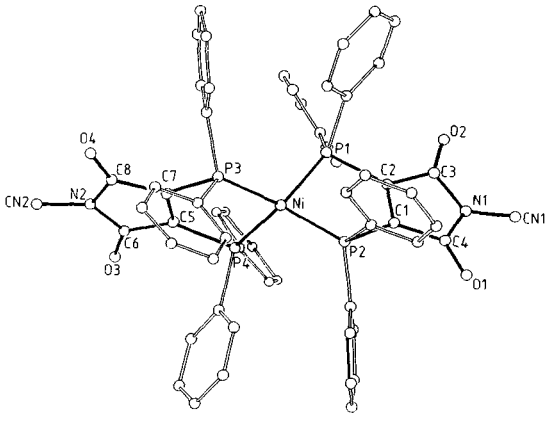


Fig. 2. Molecular structure of **5** in the crystal.

Reaction of $[(\eta^3\text{-}C_3H_5)_2Ni]$ with bis(diphenylphosphino)-*N*-methylmaleimide results, in addition to **4**, in formation of nickel complex **5**, in which both η^3-C_3H_5 groups are exchanged by bis(diphenylphosphino) ligands. An X-ray structure analysis of **5** (Fig. 2) indicates that the Ni is coordinated in a distorted tetrahedral manner by four PPh_2 groups.

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CAS Registry numbers:
1, 12240-87-8; **2**, 12077-85-9; **3**, 81423-14-5; **4**, 81408-79-9; **5**, 71277-49-1.

[1] D. Fenske, *Angew. Chem. 88* (1976) 415; *Angew. Chem. Int. Ed. Engl. 15* (1976) 381.
[3] D. Fenske, A. Christidis, *Angew. Chem. 93* (1981) 113; *Angew. Chem. Int. Ed. Engl. 20* (1981) 129.
[4] W. Bensmann, D. Fenske, *Angew. Chem. 90* (1978) 488; *Angew. Chem. Int. Ed. Engl. 17* (1978) 462.
[5] D. Fenske, A. Christidis, *Z. Naturforsch. B 36* (1981) 518.
[6] D. Fenske, K. Brandt, P. Stock, *Z. Naturforsch. B 36* (1981) 768.

Influence of Ring-Size of Cycloalkenes on the Activation Volume in the High-Pressure Copolymerization of Maleic Anhydride

By *Gérard Jenner**, *Mohamed Kellou*, and *Mihalis Papadopoulos*

Recently we reported on the high pressure kinetics of the free radical copolymerization of maleic anhydride with mono- and polysubstituted alkenes[3] in order to quantify the variations of activation volume $\Delta V^{\neq}$ with increasing steric demands of substituents (alkyl or aryl) located at the reaction center of the alkene. We introduced a new parameter, the *steric activation volume* $\Delta V_\sigma^{\neq}$, which was shown to be related to the mode and the degree of substitution, and hence may be used to predict steric effects in reaction series.

Cycloalkenes may be regarded as simple internal alkenes, since both polar and resonance factors can be considered as constant and their relative reactivities are governed mainly by steric factors. Previously, we observed that in the high-pressure copolymerization of maleic anhydride and cyclohexene, the resulting $\Delta V^{\neq}$ is more negative than expected[4]. We were therefore prompted to investigate more closely the possible $\Delta V^{\neq}$-variations with the ring size of the cycloalkene.

Table 1. Activation volumes $\Delta V^{\neq}$, steric activation volumes $\Delta V_\sigma^{\neq}$, and strain activation volumes $\Delta V_\tau^{\neq}$ for the copolymerization of maleic anhydride with cycloalkenes, as well as strain energies (SE) of the cycloalkenes.

Cycloalkene [a]	$-\Delta V^{\neq}$ [b] [cm^3/mol]	$-\Delta V_\sigma^{\neq}$ [c] [cm^3/mol]	$-\Delta V_\tau^{\neq}$ [d] [cm^3/mol]	SE [kcal/mol]
cyclopentene	30	3.7	12.3	6.9
cyclohexene	23	5.4	3.6	2.6
norbornene	28	7.5	6.5	23.6
cis-cyclooctene	32	7.4	10.6	8.8

[a] No reproducible results could be obtained in the corresponding reaction with cycloheptene. The rate of the copolymerisation with *cis*-cyclodecene is too low to be measured accurately. [b] Precision is estimated to 1–2 cm^3/mol, depending on the monomer pair. [c] Calculated. [d] Estimated.

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Table 1 shows that the activation volume ($\Delta V^{\neq}$) is not constant, although the copolymerization mechanism is the same in each case[3,4]. This change may be the result of two main factors controlling the reactivity of cycloalkenes: the strain energy of the alkene and steric hindrance due to the ring skeleton.

The activation volume ($\Delta V^{\neq}$) can be formulated as a sum[3], in the presence case as

$$\Delta V^{\neq} = \Delta V_0^{\neq} + \Delta V_\sigma^{\neq} + \Delta V_\tau^{\neq}$$

$\Delta V_0^{\neq}$ is the activation volume of the standard reaction (maleic anhydride + ethylene: -14 cm^3/mol), $\Delta V_\sigma^{\neq}$ is the steric activation volume[3], and the third term $\Delta V_\tau^{\neq}$ is the *strain activation volume* corresponding to strain associated with the ring. $\Delta V_\tau^{\neq}$ is related to a "tighter" transition state resulting from the steric interaction between monomer substituents and the propagating polymer end. $\Delta V_\tau^{\neq}$ may be roughly approximated by considering a cycloalkene as an α,β-disubstituted alkene[7] and calculating $\Delta V_\sigma^{\neq}$ from the following relationship[3]:

$$\Delta V_\sigma^{\neq} = -\omega \Psi_\sigma; \quad \Psi_\sigma = \sum_{i=1}^{n} Z_i$$

where ω is a substitution parameter, Ψ_σ a steric parameter, and Z_i is the steric value for substituent i[3].

The apparently anomalous pressure effect of $\Delta V^{\neq}$ on these copolymerizations[4] is very probably the result of ring strain. However a correlation between $\Delta V^{\neq}$ and strain energy is hard to assess (see Table 1).

Steric effects are large when adjacent parts of molecules are forced into close neighborhood by rigid groups and the possibilities of evasion are reduced to a minimum; this has an effect on the activation volume. The steric demands of substituents and/or enhanced strain energy should thus be measurable (at least for the reactions described here) as activation volume components of $\Delta V^{\neq}$. $\Delta V_\tau^{\neq}$ can be regarded as an additional volume term which gives information on the position of the transition state; steric congestion produces "late" transition states (Hammond's postulate[10]).

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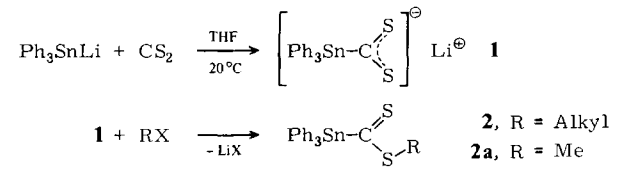
CAS Registry numbers:
Maleic anhydride, 108-31-6; cyclopentene, 142-29-0; cyclohexene, 110-83-8; norbornene, 498-66-8; *cis*-cyclooctene, 931-87-3.

[3] G. Jenner, M. Kellou, *Tetrahedron 37* (1981) 1153.
[4] M. Kellou, G. Jenner, *Makromol. Chem. 180* (1979) 1687.
[7] The ring is decomposed into two alkyl groups with the best available symmetry.
[10] W. J. Le Noble, T. Asano, *J. Am. Chem. Soc. 97* (1975) 1778.

Triphenylstannanedithiocarboxylate, a Novel Chelate Ligand**

By *Thomas Hättich* and *Udo Kunze**

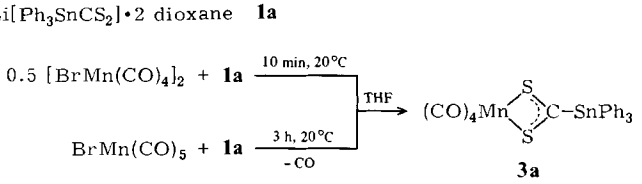
We were recently able to detect the nucleophilic addition of triphenylstannyllithium to carbon disulfide and trap the initially formed lithium salt **1** by reaction with alkyl halides[1].



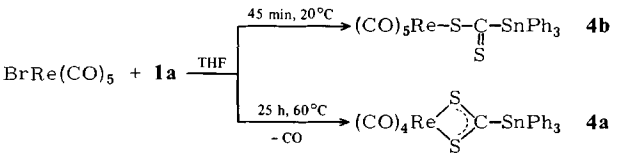
Following purification by chromatography, the alkyl stannanedithiocarboxylates **2** can be isolated as air-stable, red-violet crystals. The tin-carbon bond was verified by X-ray structure analysis.

Previously it was not possible, however, to prepare tin-functionalized dithiocarboxylato complexes from **1** and metal halides. We therefore attempted to stabilize the lithium salt **1** as a solvent adduct[2]. When the addition of CS_2 is performed in presence of dioxane, the bis(dioxane) adduct **1a** (Table 1) is obtained following removal of tetrahydrofuran (THF)[3]. **1a** crystallizes to form air- and moisture-sensitive, golden-yellow prisms (m.p. = 81–85 °C (decomp.)), which can be stored under protective gas for a few days. Using the same method we were also able to prepare the sodium **1b** and potassium salts **1c**, which are thermally more stable.

Reaction of a solution of **1a** in THF at room temperature with $[BrMn(CO)_4]_2$ or $BrMn(CO)_5$ affords, after purification by column chromatography, the stannanedithiocarboxylato(*S,S'*)-tetracarbonylmanganese complex **3a**[3] as yellow air-stable crystals (decomp. > 119 °C, m.p. = 129–131 °C).



At room temperature the pentacarbonyl complex **4b**[3] with monodentate ligand, which can be isolated as a light-pink solid (m.p. = 100 °C (decomp.)), is initially formed from $BrRe(CO)_5$. At 60 °C the analog of **3a**, the yellow chelate complex **4a**[3] (decomp. > 141 °C, m.p. = 152 °C) is obtained.



To the best of our knowledge, **3a** and **4a**, **b** are the first main-group metal substituted dithiocarboxylato complexes and are to be viewed as bonding isomers of the unstable metalodithiocarboxylates, *e.g.* $(CO)_5ReCS_2SnPh_3$, described by *Ellis et al.*[5].

The IR spectra of **3a** and **4a** (Table 1) display the four absorptions expected for a *cis*-$(CO)_4$ arrangement (C_{2v} symmetry); the antisymmetric CS stretching vibration is displaced to longer wavelengths than that of the alkyl esters **2** in consequence of the four-ring bonding scheme. Similarly, the signal of CS_2 in the ^{13}C-NMR spectrum is shifted to high field. In the mass spectrum the complete fragmentation series is observed. The IR spectrum of **4b** in CCl_4 exhibits three CO absorptions (2134 w, 2035 vs, 1999 m cm^{-1}; C_{4v}: $2A_1 + [B_1] + E$).

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Table 1. Spectroscopic data of lithium salt **1a**, methyl ester **2a**, and complexes **3a** and **4a**, **b**.

1a [a]	**2a**	**3a**	**4a**	**4b**
IR (KBr) [cm^{-1}], ν (C=O):				
		2090 m	2105 m	2133 s
		2023 s	2011 s	2072 s
		2006 vs	2002 vs	2040 vs
		1969 vs	1949 vs	2024 vs
				1981 vs
IR (KBr) [cm^{-1}], ν (CS_2):				
962 vs	1048 s	956 m	956 m	1024 s
	808 w—m			814 w
$^{13}C\{^1H\}$-NMR, δ-values, CS_2:				
218.95 [b]	266.4 [c]	224.5 [c]		
MS (m/z), 70 eV, direct inlet, calc. with ^{55}Mn, ^{120}Sn, ^{185}Re:				
	442 $[M]^+$	594 $[M]^+$	724 $[M]^+$	724 $[M-CO]^+$

[a] ^{1}H-NMR ([D$_8$]THF, TMS int.): δ = 3.53 (s, 16H, dioxane), 7.9—7.1 (mc, 15H, C_6H_5). [b] In [D$_8$]THF, TMS int.; dioxane-*C*: δ = 67.83. [c] In $CDCl_3$.

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[1] P. R. Bolz, U. Kunze, W. Winter, *Angew. Chem. 92* (1980) 227; *Angew. Chem. Int. Ed. Engl. 19* (1980) 220; U. Kunze, P. R. Bolz, W. Winter, *Chem. Ber. 114* (1981) 2744.

[2] R. Kramolowsky, *Angew. Chem. 81* (1969) 182; *Angew. Chem. Int. Ed. Engl. 8* (1969) 202.

[3] **1a**: Ph_3SnLi [4] (10 mmol) dissolved in 50 mL of THF is added dropwise over 30 min to a solution of CS_2 (10 mmol) in 10 mL of dioxane. THF is removed and the residual dioxane solution separated from precipitated LiCl. The filtrate is treated with 30 mL of diethyl ether, and if crystallization does not occur, covered with *n*-hexane (yield 59%).—**3a**, **4a**, **4b**: **1a** (1.5 mmol) is allowed to react with the stoichiometric amount of $[BrMn(CO)_4]_2$, $BrMn(CO)_5$, or $BrRe(CO)_5$ and the products purified by column chromatography (silica gel, CCl_4; yield **3a**: 75%, **4a**: 80%, **4b**: 40%).

[4] H. Schumann, K. F. Thom, M. Schmidt, *J. Organomet. Chem. 1* (1963) 167.

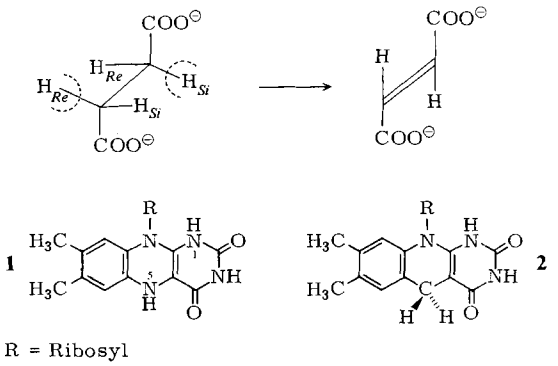
[5] J. E. Ellis, R. W. Fennell, E. A. Flom, *Inorg. Chem. 15* (1976) 2031.

Specific Transfer of the H_{Si}-Atom of Succinate to the 5-Deazaflavin Analogue of Succinate Dehydrogenase**

By *Hans-Joachim Strobel* and *János Rétey**

Succinate dehydrogenase from porcine heart mitochondria catalyzes the abstraction of an H_{Re} *and an* H_{Si}-atom of succinate[1]. Assuming an antiperiplanar conformation, this corresponds to an *anti*-elimination.

The prosthetic groups of the enzyme are covalently bound flavin and iron-sulfur clusters which transfer the electrons to ubiquinone and cytochromes. The fate of the protons abstracted is less certain. They exhibit different intramolecular kinetic isotope effects[2a], but are both washed out into the solvent. This can be explained by the fact that in the reduced form **1** of riboflavin the incoming H-atoms are bound to N-5 and N-1 and can therefore be exchanged. In 5-deazariboflavin (see **2**) an exchange of this type can be avoided[3a]. Flavin cannot be removed from succinate



dehydrogenase without denaturing the enzyme. 5-Deazaflavin was thus incorporated *via* a biosynthetic route using the flavin auxotrophic yeast mutant (HK 857b[4]). This does not grow on 5-deazariboflavin, but incorporates it into the mitochondria during aerobic incubation. Following the method of *Singer et al.*[3b], we allowed the yeast mutant to grow in the presence of riboflavin under strict anaerobic conditions. After thoroughly removing the nutrient medium, the aerobic incubation was performed in the presence of 5-deazariboflavin, whereby the yeast mitochondria were fully developed. The subsequently isolated mitochondria contained only 5-deazaflavin, manifested by their fluorescence emission spectrum and by the fact that they did not catalyze the oxidation of succinate with oxygen and artificial electron acceptors (*N*-methylphenazinium sulfate, $K_3Fe(CN)_6$).

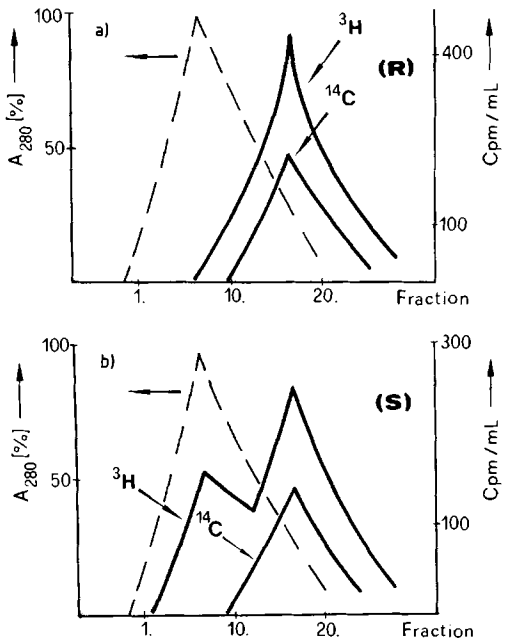


Fig. 1. Radiochromatography (—) of the 5-deazaflavin analogue of succinate dehydrogenase on Bio-Gel P-2 after incubation a) with (*R*)-[2-^{3}H, U-^{14}C] succinate and b) with (*S*)-[2-^{3}H, U-^{14}C] succinate.—The protein content was determined by absorption spectrometry (- - -).

The 5-deazaflavin-containing succinate dehydrogenase was isolated from the mitochondria by the same procedure[5] used for the natural enzyme. Natural and modified dehydrogenases from yeast exhibited similar migration rates in disc electrophoresis but different fluorescence emission spectra (λ_{max} = 520 nm and 480 nm, respectively).

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The enzyme analogue was catalytically inactive with artificial electron acceptors.

Investigation of the stereospecificity of natural succinate dehydrogenase from yeast mitochondria indicated considerable agreement with that of the enzyme from porcine heart mitochondria. Hence, the same initial ratio (2 : 1)[2a] of mono- and dideuterated succinate was found upon anaerobic incubation in D_2O. Partial oxidation of (*R*)-, (*RS*)-, and (*S*)-[2-^{3}H]succinate led to similar tritium enrichments in the unreacted substrates[2b], corresponding to a large isotope effect ($k(H_{Re})/k(T) \approx 10$) for the abstraction of H_{Re}, and to a smaller effect ($k(H_{Si})/k(T) \approx 1.5$) for the abstraction of H_{Si}.

After these preliminaries, 5-deazaflavin-containing succinate dehydrogenase was incubated with (*R*)- and with (*S*)-[2-^{3}H, U-^{14}C]-succinate. Subsequently, the main portion of the excess radioactive substrate and the stoichiometrically formed product were removed by dialysis. The residual low-molecular weight material was separated by gel chromatography of the radioactive protein on Bio-Gel P-2.

From the radioactivity (^{3}H and ^{14}C) and the protein content of the individual fractions (Fig. 1) it could be deduced that tritium was only transferred from (*S*)-[2-^{3}H]succinate to the protein. The ^{3}H/^{14}C ratio of the later fractions corresponds to that of the substrate.

The main portion of the radioactive acids was then isolated from the dialysis water using anion exchanger. Following chromatographic separation the radioactivity of the samples of succinic and malic acids (the initially formed fumaric acid was largely converted by the contaminating fumarase into L-malic acid, which, however, should not alter the radioactivity, in particular the ^{3}H/^{14}C ratio) was measured. As expected[2b], the ^{3}H/^{14}C ratio following dehydrogenation with succinate dehydrogenase decreased to approximately half the original value irrespective of the sense of chirality of the [^{3}H]succinic acid used.

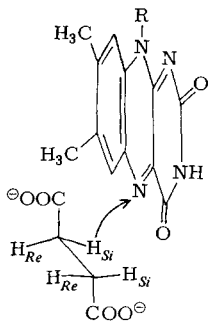

Fig. 2. Relative position of substrate and coenzyme in the active center of succinate dehydrogenase.

The steric behavior at the active center can therefore be represented as shown in Fig. 2.

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CAS Registry numbers:
2, 19342-73-5; succinate dehydrogenase, 9002-02-2; (*R*)-[2-^{3}H, U-^{14}C]-succinic acid, 81456-76-0; (*S*)-[2-^{3}H, U-^{14}C]-succinic acid, 81456-77-1.

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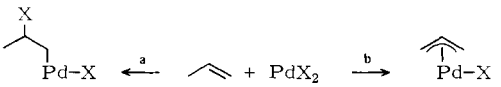
Oxidation with Palladium Salts: Stereo- and Regiospecific Acetoxylation of 4-Vinylcyclohexene Derivatives**

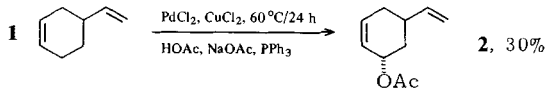
By *Andreas Heumann, Marius Reglier,* and *Bernard Waegell**

The Pd-catalyzed reaction of alkenes can proceed *via* direct addition of PdX_2 to the double bond (route a) or by abstraction of an H-atom α to the double bond (route b)[1]. It has so far remained unclear which factors determine the reaction path[2].

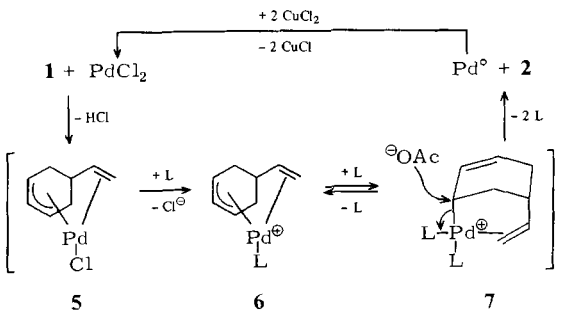


In the case of the catalytic oxidation of non-conjugated mono- and bicyclic alkadienes, exclusively route a has been reported[3]. We now report on the oxidation of related alkadienes such as **1** and **8**, which under similar conditions ($PdCl_2$ as catalyst in buffered glacial acetic acid, varying amounts of $CuCl_2$ or $CuCl_2$-LiCl-O_2) react—regioselectively and, in part, stereoselectively—according to route b.

Reaction of 4-vinylcyclohexene **1** under these conditions in the presence of excess triphenylphosphane (or "diphos") leads to formation of the allylic acetate **2**, whose structure is confirmed by ^{1}H- and ^{13}C-NMR spectroscopy, and by conversion into the unsaturated and the saturated alcohols [**2**, ^{1}H-NMR: $\delta = 1.4$—2.6 (m, 5H), 2.05 (s, 3H, OAc), 4.95, 5.04, 5.12 (m, m, m, 2H), 5.25 (m, 1H, C*H*OAc), 5.6—6.1 (m, 3H)].



The formation of the *trans*-isomer **2** and the high regioselectivity can be explained in terms of a homogeneous catalytic mechanism. The palladium(0) formed in the reaction is reoxidized by $CuCl_2$.



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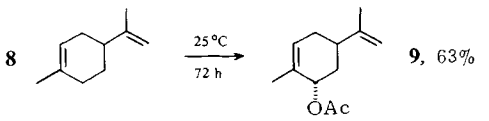
The question as to why the oxidation of **1** leads to allylic end products (route b) is difficult to answer. According to models it would seem that the course of reaction is determined not only by steric effects (proximity of the abstracted H-atom to the metal in the intermediary $PdCl_2$-**1** complex) but also by stereoelectronic effects. That the *trans*-isomer **2** is formed is understandable: The better ligand triphenylphosphane, present in excess, blocks the metal center in **7**, so that the poorer acetate-ligand can attack only from "outside"[6].

As can be seen from the mechanistic scheme, the vinyl group in **1** is decisive for the steric course of the reaction, though additional phosphane ligands appear to be necessary for the stabilization of the intermediates **6** or **7**. On increasing the nucleophilicity of the vinyl group, for example by introduction of a methyl group, the catalytic acetoxylation should take place, even in the absence of phosphanes. Indeed, reaction of limonene **8** without additional phosphane ligands (25 °C, 72 h) leads stereospecifically to α-carvyl acetate **9** (63% yield).



After modification of the limonene structure, as in 1,4-dimethyl-4-vinylcyclohexene, the acetoxylation is less selective: both isomeric acetates are formed in about equal amounts.

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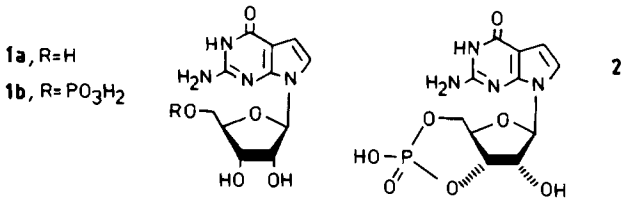
7-Deazaguanosine-3′,5′-phosphate—An Isosteric cGMP Analogue with High Affinity for Cyclonucleotide Phosphodiesterase**

By *Quynh-Hoa Tran-Thi, Doris Franzen*, and *Frank Seela**

Guanosine-3′,5′-phosphate (cGMP), like adenosine-3′,5′-phosphate (cAMP), occupies a key position in the regulation of hormone activity, but exhibits partial antagonistic functions; furthermore it activates a series of enzymes, *e.g.* protein kinases. This provided entry to the synthesis of a series of cyclonucleotide analogues[2]. Recently it has been established that cGMP is also of great importance in vision: photoactivation of one rhodopsin molecule leads to enzymic hydrolysis of 10^5 cGMP molecules[3]. Incubation of intact cells with cyclonucleotides produced no or only slight activity; because of their negative charge they can only penetrate the cell membrane with difficulty. In consequence, cyclonucleotides with lipophilic groups, *e.g.* butyryl residues, were synthesized. We report here the synthesis and properties of the first 7-deaza-cGMP analogue.

Pyrrolo[2,3-*d*]pyrimidine nucleosides are more lipophilic than the corresponding purine compounds, since they do not contain an N atom in the 7-position. Furthermore, the 7-deaza derivative of guanosine is the only ring-modified guanosine analogue of which naturally occurring derivatives have been found. We recently synthesized 7-deazaguanosine **1a** by phase transfer catalysis[6]. In contrast to guanosine, the more lipophilic compound **1a** shows no tendency to aggregate, thus increasing its availability in aqueous solution.



Phosphorylation of **1a** with PCl_3O in trimethyl phosphate leads regioselectively to the 5′-monophosphate **1b** [^{31}P-NMR (D_2O): $\delta = 3.17$], which can be cyclized with *N,N*-dicyclohexylcarbodiimide in pyridine yielding the cyclophosphate **2**. Subsequent anion-exchange chromatography and lyophilization produces pure **2** [^{31}P-NMR (D_2O): $\delta = 9.40$] as the amorphous triethylammonium salt. The structure of **2** is confirmed by its ^{1}H-NMR spectrum. The fused cyclophosphate ring results in angular distorsion of the β-D-ribofuranosyl residue and hence the 1′-proton does not participate in vicinal coupling, a result which is also found with cGMP.

Cyclophosphate-specific phosphodiesterase cleaves the cyclonucleotide **2** to afford the 5′-monophosphate **1b**. Table 1 shows that **2** is hydrolyzed more rapidly than cGMP. The 7-purine nitrogen is thus not a requirement for the binding of cGMP[8] and its analogues to the phosphodiesterase and their hydrolysis by this enzyme, a phenomenon which is also found with tubercidin-3′,5′-phosphate[10a].

Table 1. Relative initial rates of the enzymic hydrolysis of purine and 7-deazapurine nucleoside-3,5′-phosphates with cyclonucleotide phosphodiesterase from bovine heart.

Compound	Relative initial rates of hydrolysis
7-deazaguanosine-3′,5′-phosphate **2**	3.2
cGMP	1.9
tubercidin-3′,5′-phosphate	1.4
cAMP	1.0

In contrast to cGMP, **2** does not aggregate in aqueous solution; we presume that this is due to the absence of the 7-purine nitrogen, avoiding Hoogsteen base-pairing, which causes the aggregation in guanidine nucleotides.

The higher rate of hydrolysis of **2**, which is not achieved by other cGMP derivatives, may be due to the following: 1) increased availability of **2** due to diminished aggregation, 2) increased affinity of the more hydrophobic substrate to the active center of the phosphodiesterase, and 3) increased ring strain in the cyclophosphate residue in-

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duced by the chromophore through the highly stable *N*-glycosylic bond.

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Sterically Crowded Ethanes and Ethenes from Tri-*tert*-butylsilylmethyl Carbenoids**

By *Manfred Weidenbruch** and *Hermann Flott*

Ethanes[1] and ethenes[2] with bulky substituents are suitable as models for the investigation of unusual bonding situations, which manifest themselves for example, in large atomic distances, widened bond angles, unexpected conformations, and twisting of the CC double bond. We have found a facile entry to 1,2-disilyl derivatives of this class of compounds *via* reaction of methyllithium with tri-*tert*-butyl(dihalomethyl)silanes.

Thus, reaction of tri-*tert*-butyl(dibromomethyl)silane **1**[3] with methyllithium leads, *via* the carbenoid **2** to (*E*)-bis(tri-*tert*-butylsilyl)ethene **3** together with 1,2-dibromo-1,2-bis(tri-*tert*-butylsilyl)ethane **4** and (bromomethyl)tri-*tert*-butylsilane **5**[4].

$$(t\text{-}C_4H_9)_3SiCHBr_2 + LiCH_3 \longrightarrow \underset{\mathbf{2}}{\{(t\text{-}C_4H_9)_3SiCHBrLi\}} + CH_3Br$$
1

$$\xrightarrow[-2\ LiBr]{\times 2} (t\text{-}C_4H_9)_3SiCH{=}CHSi(t\text{-}C_4H_9)_3 \quad \mathbf{3}$$

$$\mathbf{2} \xrightarrow[-LiBr]{+\mathbf{1}} (t\text{-}C_4H_9)_3SiCHBrCHBrSi(t\text{-}C_4H_9)_3 \quad \mathbf{4}$$

$$\longrightarrow (t\text{-}C_4H_9)_3SiCH_2Br \quad \mathbf{5}$$

A further route to **3** is the partial lithiation of **4** with intramolecular elimination of LiBr. Repeated reaction of methyllithium with **5** yields 1,2-bis(tri-*tert*-butylsilyl)ethane.

Unlike **1**, which exclusively exchanges Br for Li, its dichloro analog[3] reacts with methyllithium preferably with H/Li exchange *via* the carbenoid **8** to give (*E*)-1,2-bis(tri-*tert*-butylsilyl)-1,2-dichloroethene **9**.

$$(t\text{-}C_4H_9)_3SiCHCl_2 + LiCH_3 \rightarrow \underset{\mathbf{8}}{\{(t\text{-}C_4H_9)_3SiCCl_2Li\}} + CH_4$$

$$2\ \mathbf{8} \rightarrow \underset{\mathbf{9}}{(t\text{-}C_4H_9)_3SiCCl{=}CClSi(t\text{-}C_4H_9)_3}$$

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The X-ray structure analysis (Fig. 1) of **4** illustrates quite nicely the unusual bonding features in the sterically congested ethanes and ethenes prepared so far.

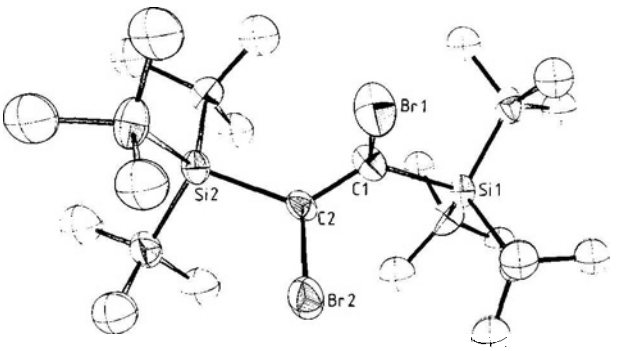

Fig. 1. Structure of **4** in the crystal.

As in other highly-branched C_t—C_t hydrocarbons[1] the molecule **4** exists in the D,L-*gauche* form. Consistent with empirical force field calculations[7] the tri-*tert*-butylsilyl groups have C_3 local symmetry. The C1—Si1 and C2—Si2 bonds of 196 and 200 pm, respectively, are markedly longer than the normal value (187 pm), whereas the central C1—C2 bond is only *ca.* 150 pm in length. The bond angles Si1C1C2 and Si2C2C1 of 128.6 and 126.9°, respectively, are much greater than those found in all previously known highly-branched hydrocarbons.

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Black Lipid Membranes from Polymerizable Lipids**

By *Roland Benz, Werner Prass,* and *Helmut Ringsdorf**

The stabilization of model membranes *via* polymerization of lipid molecules has been investigated up to now in monolayers and liposomes[6]. Polymerizations in planar bimolecular black lipid membranes (BLMs), another model system for membranes, have not yet been described. The great disadvantage of BLMs as model membranes is their lack of long-term stability: depending on the lipid and the

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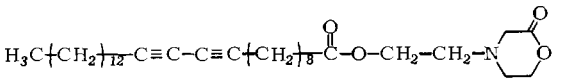
[**] Polyreactions in Oriented Systems, Part 25.—Part 24: H. Ringsdorf, H Schupp, *J. Macromol. Sci. Chem. A 15* (1981) 1015

conditions used for their preparation, they are stable only for minutes or hours. We report here efforts to stabilize BLMs by polymerization of lipid molecules in planar bilayer membranes.

In a preliminary study, several synthetic lipids and lysolipids containing polymerizable acrylic, butadiene, or diacetylenic units either in the hydrophobic part or in the hydrophilic part of the molecule were observed to form BLMs. The membrane resistance and capacitance of the BLMs formed from **3**, **4**, and **8**, which are stable for more than 5 min, are shown in Table 2. The measured values are compared with values obtained for BLMs from purified egg lecithin[13].



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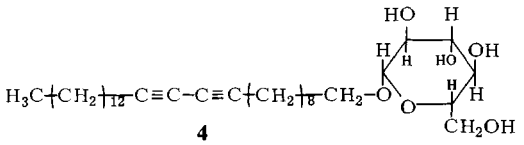

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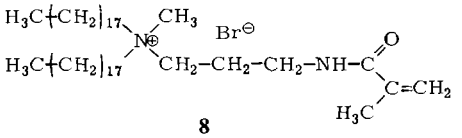

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Table 2. Lifetime, electrical resistance, and capacitance of black lipid membranes from polymerizable lipids **3**, **4**, and **8**.

Compound	T [°C]	Lifetime	Resistance [Ω cm²]	Capacitance [μF/cm²]
Egg Lecithin	20	2—3 h	10^7-10^8	0.33 ± 0.02
3	25	1—3 h	10^7-10^8	0.31 ± 0.02
4	40	1—2 h	10^7	—
8	21	5—10 min	10^6	0.38 ± 0.04

Attempts to achieve UV-sensitized polymerization of BLMs from the two diacetylenic compounds **3** and **4** were unsuccessful. This can be explained by the fact that the formation of stable black lipid membranes is possible only in the liquid-analogous state. On the other hand, polymerization of diacetylene-containing lipids is topochemically controlled, and thus takes place only in the solid-analogous state[16]. Furthermore, methacrylamide derivatives do not only polymerize in the solid-analogous state[6]. The free-radical polymerization of **8** was initiated by UV irradiation of methyl azoisobutyrate dissolved in the membrane.

The progress of the reaction can be followed by measuring the change in the charging current (capacitance). This is shown schematically in Figure 3.

During UV irradiation, optical changes were not observed in the membranes: nevertheless, their capacitance rose from 0.38 μF/cm² to the very high value of 2 μF/cm². This was observed on the oscilloscope trace as a slower current-decrease, corresponding to a higher capacitance (see Fig. 3b). The current did not return to zero after 0.5—2 min, and the plateau value increased slowly over *ca.* 20 min (see Fig. 3c). The resistance of the membrane, which had still not undergone an optical change, therefore, decreased markedly. In the final stage of the polymerization—after *ca.* 20 min—the measured resistance was only *ca.* 20% more than that of the electrolyte solution itself. These results can be explained by changes in the structure

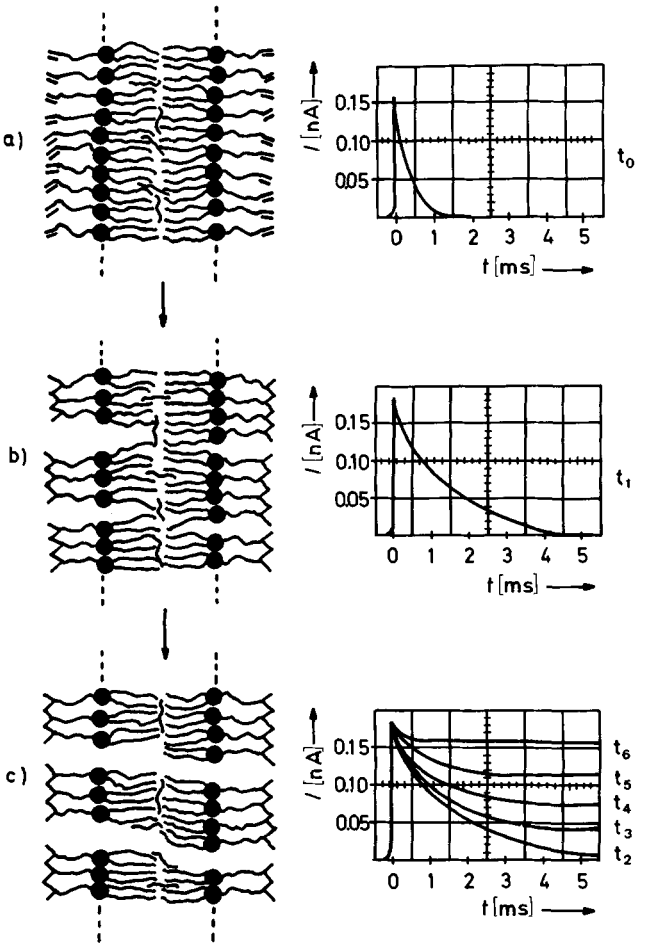

Fig. 3. Schematic representation of the structural changes in the membrane and course of charging currents (measurement of capicitance) during polymerization: a) monomeric membrane before UV irradiation ($t = t_0$); b) membrane at the beginning of the polymerization ($t = t_1 = 0$ min); c) polymeric membrane and change in current across the membrane with time ($t_2 = 1$ min, $t_6 = 20$ min).

of the polymeric black lipid membrane (shown schematically in Fig. 3). Because the polymerization occurs at the surface of the bilayer, the lipid head-groups are drawn together. Thus, the membrane becomes "thinner" at some points and water can enter the hydrophobic part of the bilayer. This causes an increase in the dielectric constant (ε_M) of the membrane, leading to a higher capacitance.

The strain on the membrane surface during polymerization finally leads to formation of holes in the polymer membrane (see Fig. 3c) and hence to the low electrical resistance of the polymerized bilayer. The product of the reaction is a bilayer net, which still has remarkable mechanical stability and has a lifetime of up to 50 min after the polymerization. In contrast to this slow membrane collapse, the rupture of a typical monomeric BLM after its induction is complete within a fraction of a second.

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Regioselective Acylamination by Hetero-Cope Rearrangement**

By *Richard Höfelmeier* and *Siegfried Blechert**

The direct amination of substituted arenes can be accomplished in some cases with electrophilic aminating reagents or by rearrangement reactions, but often presents problems as a result of unsatisfactory regioselectivity or poor yields[4]. We therefore searched for a generally applicable method void of these disadvantages. Numerous [3,3]-sigmatropic rearrangements have proven useful for *o*-alkylation; however, corresponding hetero-Cope rearrangements for *o*-amination have, to our knowledge, previously never been investigated. From the results of *Sheradsky et al.*[8] and also of *Coates et al.*[9] it can be concluded that *N*-aryl-*O*-vinylhydroxylamines are suitable for [3,3]-sigmatropic rearrangements.

We found that the hydroxamic acids **1**, readily obtainable from *N*-phenylhydroxylamines[11], are good educts for regioselective acylaminations: Reaction of the sodium salts **2** with imidoyl chlorides **3** directly affords the *o*-phenylenediamine derivatives **6** (**1**→**2**: suspension of NaH in tetrahydrofuran; **2**→**6**: after addition of **3**, 2–6 hours stirring at room temperature).

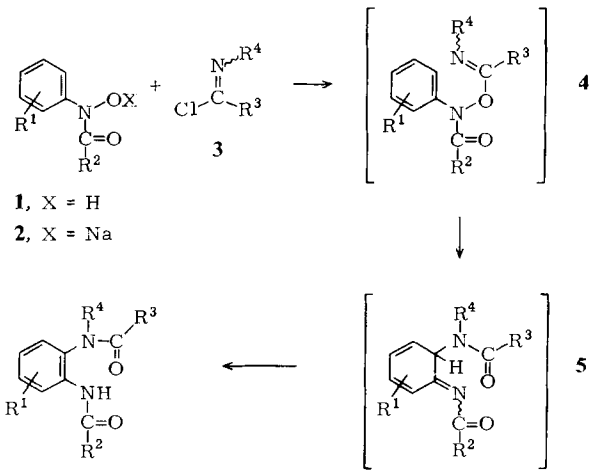

Table 1. Synthesized *o*-phenylenediamine derivatives **6**. $R^3 = p\text{-}O_2NC_6H_4$ (in the case of **6c**: C_6H_5).

	R^1	R^2	R^4	Yield [%]
6a	H	$OCH_2C_6H_5$	CH_3	75
6b	H	$OCH_2C_6H_5$	C_2H_5	80
6c	4-CH_3	CH_3	CH_3	65
6d	4-CH_3	CH_3	C_2H_5	60
6e	4-CH_3	CH_3	C_6H_5	15
6f	4-OCH_3	CH_3	CH_3	65
6g	4-Cl	CH_3	CH_3	80

In no case were the plausible intermediates **4** isolable. However, in HPLC studies of the reaction we were able to observe the formation of an apolar product, also unstable at −25 °C, which is rapidly converted into **6**. Our findings so far point to a [3,3]-sigmatropic rearrangement, which, however, differs somewhat from the rearrangement of the "heteroanalogous" **4**, =O instead of $=NR^4$, and **4**, $-SO_2R^3$ instead of $-C(NR^4)R^3$[12].

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The method described here thus enables an arene to be regioselectively substituted under mild conditions with acylamino groups. But the method is unsuitable for the incorporation of an acylamino group (see **6e**).

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[9] R. M. Coates, I. Md. Said, *J. Am. Chem. Soc. 99* (1977) 2355.
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λ^3-Phosphorins by [4+2]-Cycloaddition of α-Pyrones and Cyclopentadienones with $H_5C_6—C{\equiv}P$

By *Gottfried Märkl**, *Gui Yu Jin*, and *Ernst Silbereisen*

Until now only a few or no [2+2]- or [2+4]-cycloaddition reactions, respectively, involving the participation of the —P=C-group have been described for λ^3-phosphaalkenes and aromatic λ^3-phosphorus heterocycles. To the best of our knowledge the first cycloaddition of an open-chain phosphaalkene was achieved by *Bickelhaupt et al.* in the reaction of *P*-mesityl(diphenylmethylene)phosphane with mesityl nitrile oxide as 1,3-dipole[8,9].

We now report for the first time the [2+4]cycloadditions of *P*-chloro(α-trimethylsilylbenzylidene)phosphane **1**[13] or of the benzylidynephosphane (2-phenylphosphaethyne) **5** to α-pyrones **2** and cyclopentadienones **8**.

α-Pyrones react with **1** in the presence of KF/[18]crown-6 at 220 °C in a bomb tube (undiluted or in *o*-dichlorobenzene) to afford the λ^3-phosphorins **3**.

The reaction conditions allow us to presume that the Diels-Alder adduct **4** is not formed, but rather that **1** is firstly converted into **5**, which was recently synthesized by *Appel et al.*[14] by thermolysis of **1** at 800 °C, and is stable up to −50 °C. **5** and **2** react *via* the cycloadduct **6** to yield

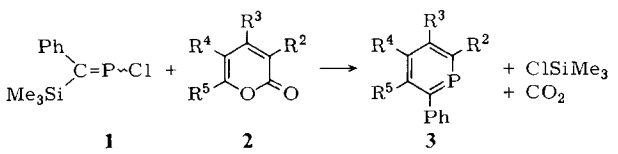

Table 1. λ^3-Phosphorins **3** from methylenephosphanes **1** (*via* **5**) and α-pyrones **2** (molar ratio 1 : 1) [22] (selection).

Comp.	R^2	R^3	R^4	R^5	M.p. [°C]	Yield [%] [a]
3a [21]	Ph	Ph	Ph	Ph	252–255	16
3b	H	Ph	Ph	Ph	172–175	9
3c [21]	H	Ph	H	Ph	130–132	14
3d [b]	H	Ph	Ph	H	164–165	16
3e	H	H	H	Ph	oil	10

[a] Relative to amounts of **2** used, a fraction of which was reisolated. [b] ^{1}H-NMR ($CDCl_3$): $\delta = 8.52$ (d, H-2, $^2J_{PH} = 38$ Hz), 7.88 (d, H-5, $^3J_{PH} = 6$ Hz), 6.67–7.58 (m, C_6H_5).

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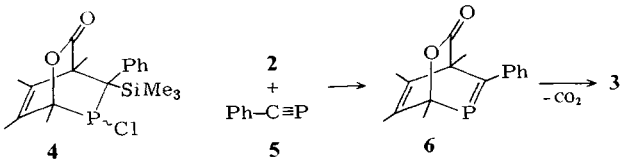
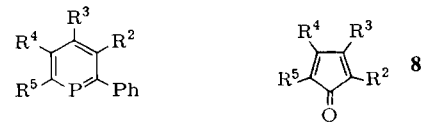
3. Isomers of type 7 were not detected. By means of this method 2,3-disubstituted, 2,4,5-trisubstituted, and 2,3,4,5-tetrasubstituted λ^3-phosphorins **3** have become accessible (Table 1).



4 **5** **6**

By analogy to α-pyrones **2**, cyclopentadienones **8** react with **5** *via* elimination of CO to furnish pentasubstituted λ^3-phosphorins (*e.g.* **3f**, $R^2=R^5=C_2H_5$, $R^3=R^4=C_6H_5$, m.p. = 182–184 °C; **3g**, $R^2=R^5=CH_3$, $R^3=R^4=C_6H_5$, m.p. = 179 °C).



7 **8**

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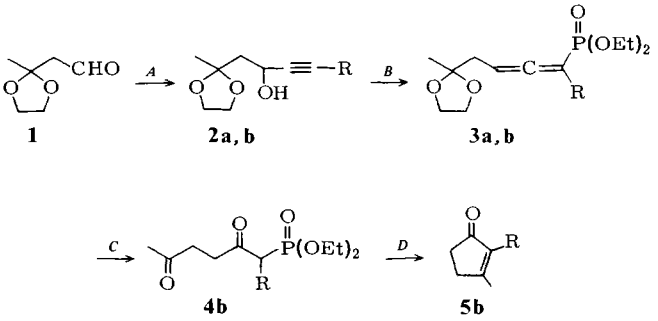
[22] With assistance from G. Dorfmeister and I. Trötsch.

β,ε-Dioxophosphonates by Reductive Nucleophilic Acylation of 1,3-Dioxo Compounds: Facile Synthesis of Jasmones**

By *Hans-Josef Altenbach** and *Rainer Korff*

The cyclization of 1,4-diketones is still the widest applicable method for the synthesis of cyclopentenones; in place of the classical aldol condensation, Wittig- and Wittig-Horner-reactions have also found application for the ring closure. A method developed by us to provide easy excess to β-oxophosphonates by reductive nucleophilic acylation of ketones or aldehydes[4] stimulated attempts to prepare the β,ε-dioxophosphonates (type **4**), suitable as educts for such cyclizing olefination reactions, from partially protected 1,3-dioxo compounds (type **1**). The method is outlined here, using the synthesis of dihydrojasmone **5b** and dehydrojasmone **5c** as examples.

The protected 3-oxobutanal **1**[6], easily accessible from ethyl acetoacetate, served as educt for **5b** and **5c**. For the synthesis of the dihydrojasmone **5b**, **1** is transformed into the alkynol **2b**, from which the α-pentyl-substituted allenephosphonate **3b** is formed *via* the phosphorous acid ester by propargyl rearrangement[7]. The addition product obtained from **3b** on reaction with sodium ethoxide is hydrolyzed with hydrochloric acid to the β,ε-dioxophosphonate **4b**, previously prepared *via* another route[3a]. The intramolecular olefination of **4b** to **5b** can be realized (yield 60%) with sodium hydride in tetrahydrofuran (THF), as already mentioned by *Heathcock et al.*[3a].

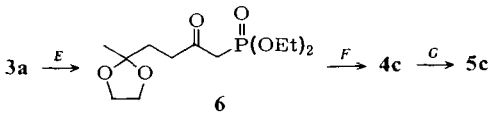


1 **2a, b** **3a, b** **4b** **5b**

a, R = H; **b**, R = *n*-C_5H_{11}; **c**, R = $CH_2C{\equiv}CC_2H_5$

A 1) LiC≡CR in THF, −78 °C, 2) NH_4Cl; *B* $ClP(OEt)_2$, Et_3N, CH_2Cl_2 (14 h, room temperature) [**3b**: short-path distillation 120 °C/0.1 torr, yield 88%]; *C* 1) 2 h reflux with NaOEt in EtOH, 2) 10% HCl (0.5 h, room temperature); *D* NaH in THF (12 h, room temperature).

In the synthesis of the dehydrojasmone **5c**, the unsaturated side chain was not incorporated during the alkynation step, but at a later stage. This is possible, since the allenephosphonate **3a** can by hydrated to the β-oxophosphonate **6** by reaction with diethylamine in ether followed by hydrolysis, without the ketal function being cleaved.



6

$R=CH_2C{\equiv}CC_2H_5$

E 1) $HNEt_2$ in Et_2O (12 h, room temperature), 2) 30% aqueous NH_4Cl solution, Et_2O (4 h, room temperature) [**6**: b.p. 134–136 °C/0.3 torr, yield 62%]; *F* 1) NaH or $KN(SiMe_3)_2$, 2) RBr, 3) 10% HCl, Et_2O (24 h, room temperature) [chromatography: silica gel/ethyl acetate; **4c**: short-path distillation 90–100 °C/0.4 torr, yield 48%]; *G* $NaN(SiMe_3)_2$ in THF (2 h, room temperature).

The anion of **6** is (partially) dialkylated by 1-bromo-2-pentyne. The desired compound **4c** can, however, be isolated by column chromatography after hydrolysis of the ketal function, and then cyclized with sodium bis(trimethylsilyl)amide to give **5c** (yield 62%).

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[**] Phosphorus- and Sulfur-Substituted Allenes in Synthesis, Part 2.—Part 1: [4].

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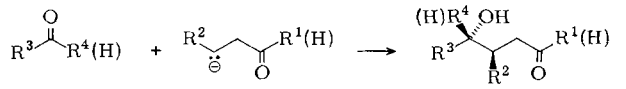
Diastereoselective Homoaldol Reaction with a (1-Oxycrotyl)aluminum Compound, a Homoenolate Equivalent of *n*-Butanal**

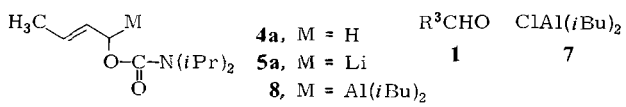
By *Dieter Hoppe** and *Florian Lichtenberg*

We recently reported[1] the first more general preparative solution to the transformation aldehyde- or ketone-homoenolate **2** + carbonyl compound **1** → homoaldol **3**.



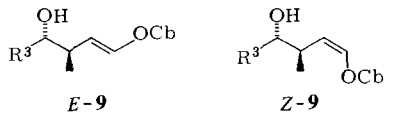
1 **2** **3**

Stereocontrolled homoaldol reactions[4] have been successfully performed using the *E*-(1-carbamoyloxy)crotylaluminum derivative **8**[15]: **8**, obtained by transmetalation of the lithium compound **5a** with excess **7**, adds to aldehyde **1** at −78 °C to afford δ-hydroxyenol carbamates **9** and **10**. Of the four possible diastereomers, the homofacial[10b] (*threo*-configurated[10]) adducts *E*- and *Z*-**9** (rel. yields 83—97%) predominate; only 2—16% of the heterofacial[10b] (*erythro*)-diastereomers *E*-**10** are formed (cf. Table 1).

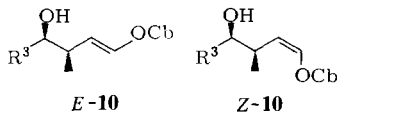


4a, M = H
5a, M = Li
8, M = Al(*i*Bu)$_2$

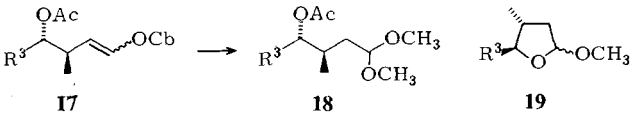
R^3CHO **1** $ClAl(iBu)_2$ **7**



E-**9** *Z*-**9**



E-**10** *Z*-**10**



17 **18** **19**

a, R^3 = $(CH_3)_3C$, **b** = CH_3, **c** = $(CH_3)_2CH$, **d** = C_6H_5

Cb = $C(=O)N(iPr)_2$

Table 1. Synthesis of adducts **9** and **10** by addition of crotylaluminum compound **8** to aldehydes **1**.

9/10 [a]	Yield [%] [b]	Ratio of diastereomers [c] *E*-**9** : *Z*-**9** : *E*-**10** : *Z*-**10**	*threo* : *erythro* [10]
a	90	87 : 10 : 2 : <1	97 : 3
b	88	78 : 13 : 8 : <1	91 : 9
c	90	90 : 4 : 5 : <1	94 : 6
d	95	77 : 6 : 16 : <1	83 : 17

[a] Satisfactory CH analyses were obtained. [b] After chromatographic purification [1]. [c] Determined by capillary gas chromatography. We thank Dr. *Helga Ludwig-Köhn*, Göttingen, for her advice.

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[**] Metalated Nitrogen Derivatives of Carbonic Acid in Organic Synthesis, Part 21. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 20: [1].

Enol esters **9** and **10** are stable to acid; esters **9** and methanol/methanesulfonic acid react under mercuric acetate catalysis (1 mol%) to form lactol ethers **19**. Thus, **19c** is formed in 79% yield from *E*-**9c** after 4 h at 25 °C. Analogously the acetates **17** deliver the dimethyl acetals **18**; *e.g.* *E*-**17c** affords **18c** in 86% yield after 12 h at 25 °C. **18** and **19** are easy to handle, protected derivatives of γ-hydroxyaldehydes **3**. Hence, **8** acts as a diastereoselectively-reacting synthetic equivalent for the unknown homoenolate of *n*-butanal **2** (R^1 = H, R^2 = CH_3).

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[1] D. Hoppe, R. Hanko, A. Brönneke, F. Lichtenberg, *Angew. Chem. 93* (1981) 1106; *Angew. Chem. Int. Ed. Engl. 20* (1981) 1024.
[4] For a further method cf. R. Hanko, D. Hoppe, *Angew. Chem. 94* (1982) 378; *Angew. Chem. Int. Ed. Engl. 21* (1982) 372.
[10] Only one enantiomer is shown.—In the *threo/erythro* terminology we concur with *Heathcock*. For discussions cf. a) D. Seebach, J. Goliński, *Helv. Chim. Acta 64* (1981) 1413; b) W. Kreiser, *Nachr. Chem. Tech. Lab. 29* (1981) 555.
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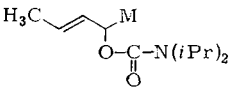
Highly Diastereo- and Regioselective Homoaldol Reactions with (1-Oxyallyl)titanium Derivatives**

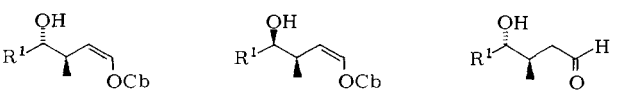
By *Rudolf Hanko* and *Dieter Hoppe**

We have reported the stereoselective addition of the crotylaluminum derivative **3** to aldehydes **6**[1], and now describe a particularly effective variant of the homofacial (*threo*-selective)[1] homoaldol reaction. Allowing the lithium compound **2**, obtained (as are in general homoenolate equivalents of this type) by deprotonation of the *E*-crotyl carbamate **1** with *n*-butyllithium (*n*-BuLi)[2], to react with chlorotris(diethylamino)titanium **5**[3] afforded the crotyltitanium derivative **4**[4]. At −78 °C **4** adds to aldehyde **6** to form almost exclusively the *Z*-configurated



$ClTi(NEt_2)_3$ **5** $R^1CH{=}O$ **6**

1, M = H, **2**, M = Li
3, M = Al(*i*Bu)$_2$ **4**, M = $Ti(NEt_2)_3$



Z-**7** *Z*-**8** **9**

Cb = $C(=O)N(iPr)_2$

(*threo*)-δ-hydroxyenol carbamate[5] *Z*-**7** (cf. Table 1), in addition to 0—3.0% of *Z*-**8** (*erythro*)[1] in the crude product; the fraction of the remaining regio- and stereoisomers is

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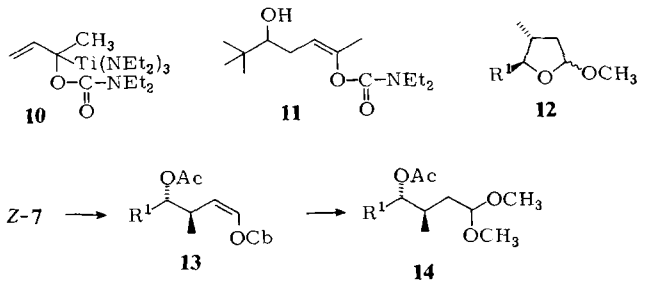
Table 1. Synthesis of esters *Z*-7 [a, b] by addition of the crotyltitanium compound **4** to aldehydes **6**.

	R¹	Yield [%] [c]	*Z*-7 : *Z*-8 [d, e]	^{1}H-NMR of *Z*-7 [f] H-4 [δ-values]	$J_{3,4}$ [Hz]
a	$(CH_3)_3C$	92	99.5 : <0.5	3.08	2.5
b	CH_3	92	97.6 : 2.4	3.58	6.0
c	$(CH_3)_2CH$	96	97.5 : 2.5	3.00	5.0
d	$(CH_3)_2C{=}CH$	96	97.0 : 3.0	4.10	5.5

[a] Satisfactory CH analyses obtained. [b] Racemic mixtures. [c] Crude product homogeneous according to ^{1}H-NMR and thin layer chromatography. [d] Determined by capillary gas chromatography [1]. [e] Poorest value from two or three experiments. When freshly prepared **5** was used, the fraction of *Z*-**8** decreased to approx. half these amounts. [f] In CCl_4.

less than 1% (detected by gas chromatography[1]). A high regioselectivity of the carbonyl addition is also observed with 1-alkylated derivatives; thus, **10** and 2,2-dimethylpropanal **6a** react to form the γ-adduct **11** free of isomers (yield 87%). Methanolysis of the enol ester *Z*-**7** (methanol, 1 equiv. methanesulfonic acid, 1 mol% Hg(II) acetate, 25 °C)[1] affords the lactol ether **12**. Dimethyl acetals **14** were obtained analogously *via* acetates **13**[1]. **12** and **14**



are versatile, useful derivatives of homoaldol **9**. Hence, a method is thus available for the homoaldol reaction (to our knowledge the only[1]) which is just as efficient as the best variants of the aldol reaction.

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[1] D. Hoppe, F. Lichtenberg, *Angew. Chem. 94* (1982) 378; *Angew. Chem. Int. Ed. Engl. 21* (1982) 372; and literature cited therein as well as stereochemical correlations and terminology.

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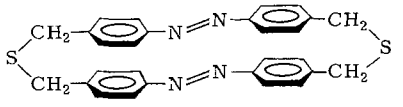
[4] Synthetic applications of allyltitanium reagents: a) F. Sato, S. Iijima, M. Sato, *Tetrahedron Lett. 22* (1981) 243; b) M. T. Reetz, R. Steinbach, J. Westermann, R. Peter, *Angew. Chem. 92* (1980) 1044; *Angew. Chem. Int. Ed. Engl. 19* (1980) 1011; c) B. Weidmann, L. Widler, A. G. Olivero, C. D. Maycock, D. Seebach, *Helv. Chim. Acta 64* (1981) 357; d) F. Sato, K. Iida, S. Iijima, H. Moriya, M. Sato, *J. Chem. Soc. Chem. Commun. 1981*, 1140; e) M. T. Reetz, R. Steinbach, J. Westermann, R. Urz, B. Wenderoth, R. Peter, *Angew. Chem. 94* (1982) 133; *Angew. Chem. Int. Ed. Engl. 21* (1982) 135; f) B. Klei, J. H. Teuben, H. J. de Liefde Meijer, *J. Chem. Soc. Chem. Commun. 1981*, 342.

[5] *General procedure. Z*-7: 1.1 equiv. of **5** as a *ca.* 1 M solution in hexane is added to a *ca.* 0.3 M solution of **2** [2] in ether/hexane under N_2 at −78 °C, the mixture stirred for 1 h at −78 °C, and 1.0–1.1 equiv. of **6** then added. After 30 min at this temperature, the cold reaction mixture is poured into 10 mL (per mmol **2**) of 2 N hydrochloric acid/ether (1:1 v/v), the aqueous layer extracted with ether, the ether removed, and the combined extracts washed with $NaHCO_3$ and KCl solutions. After drying ($MgSO_4$) and removal of the solvent *in vacuo*, almost pure *Z*-**7** is obtained (Table 1).

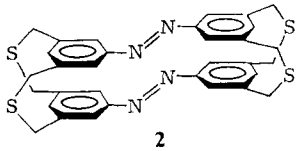
Azobenzene Phanes**

By *Dieter Gräf, Helmut Nitsch, Dieter Ufermann, Gisela Sawitzki, Helmut Patzelt,* and *Hermann Rau**

We have synthesized 2,19-dithia[3.3](4,4′)-*trans*-diphenyldiazeno(2)phane **1** and 2,19,36,39-tetrathia[3.3.3.3]-(3,3′,5,5′)-*trans*-diphenyldiazeno(4)phane **2**, the first azobenzene phanes, in order to study the interactions of the azobenzene electron systems and to investigate the *trans-cis* isomerization. **1** and **2** are potential precursors of molecules containing the tetraazacyclobutane moiety.



1



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Cyclization of 4,4′-bis(bromomethyl)azobenzene with Na_2S (high dilution)[1] afforded **1** as a yellow powder in 40% yield (crude yield 80%)[2a]. Likewise[1], alkaline condensation of 3,3′,5,5′-tetrakis(mercaptomethyl)azobenzene with 3,3′,5,5′-tetrakis(bromomethyl)azobenzene under high dilution conditions furnished **2** (crude yield 60%)[2b]. X-ray structure analysis[3] indicated that **1** has point symmetry and parallel *trans*-azo groups; the benzene rings are inclined *ca.* 20° relative to one another. Bond-lengths and -angles are similar to those of azobenzene. The separation of the azo groups is 386 pm and that of the center of gravity of the benzene rings 357 pm (only slightly more than the "thickness" of the aromatic π-system[4]).

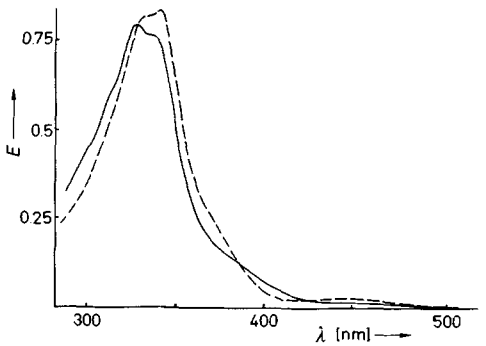

Fig. 1. Absorption spectrum of **1** (---), $c = 1.6 \times 10^{-5}$ mol/L in benzene and **2** (—), *c* not determined, in toluene.

In contrast to 4,4′-dimethylazobenzene **3**, the UV π→π* bands of **1** and **2** (Fig. 1) are split: increasing hypsochromic shift of the intense short wavelength component band (0—0 transition in **3**: 360 nm; **1**: 344 nm; **2**: 339 nm) and bathochromic shift of the typically weak phane band (**1**: *ca.* 380 nm; **2**: *ca.* 395 nm) are observed. The vibrational structure of the short wavelength component band is

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characteristic of phanes (used as a criterion in the isolation procedure) and can be interpreted as arising from the increased rigidity of the molecular framework relative to that of simple azobenzenes. The long wavelength $n \rightarrow \pi^*$ bands at 450 nm become weaker with increasing planarity of the azobenzene units in the series **3**→**1**→**2**; interactions between the n orbital systems cannot be established with certainty.

1 and **2** isomerize under the action of light[5]. This is experimental proof that *trans-cis*-photoisomerization of azobenzenes can occur by inversion of the bond angle at nitrogen.

By means of kinetic analysis of irradiation experiments in highly dilute solutions we have obtained evidence for the possible formation of tetraazacyclobutane: Apart from the *trans-cis* isomerizations an additional reaction, which is not very important compared to the isomerizations, is observed that leads to a molecule forming the phanes quantitatively, unless $\lambda_{exc} < 320$ nm whereupon the azo groups are destroyed (azobenzene and bis-(*p*-benzeneazotolyl)sulfide are stable under these conditions). At present we are investigating the irradiation of powders (analysis by photoacoustic spectroscopy) and of crystals (X-ray structure analysis).

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[2] a) **1**: Chromatography on Sephadex LH 20 and SiO_2 (40 °C, dimethylformamide and benzene, respectively), and crystallization by slow (8 weeks) evaporation of toluene as solvent; above 230 °C red, above 275 °C dark red, does not melt up to 310 °C; solubility; *ca.* 10^{-5} mol/L in *n*-hexane and EtOH, *ca.* 2×10^{-4} mol/L in toluene, readily soluble in acids; ^{1}H-NMR ($CDCl_3$): $\delta = 7.43$, 7.33, 7.13, 7.03 (q, aromat. H), 3.89 (s, CH_2); MS: *m/z* 480, 194, 210, 120, 227, 254, 181, 240, 526, 135; FD-MS *m/z*: 480; b) **2**: Chromatography on SiO_2 with CH_2Cl_2; change of color above 250 °C, decomp. *ca.* 290 °C; insoluble in *n*-hexane and EtOH, sufficient amounts for spectroscopy in supersaturated solutions of toluene, CH_2Cl_2, and $CHCl_3$, dry samples insoluble; readily soluble in H_2SO_4 and CF_3COOH with slow decomposition; ^{1}H-NMR ($CDCl_3$, supersaturated): $\delta = 7.31$, 7.22 (d, aromat. H (2 : 1)), 3.98 (s, br. CH_2) MS: *m/z* 596, no fragmentation; high resolution [2c]: *m/z* 596.1196 (calc.), 596.1195 (found); c) we thank Dr. Rodzinski, Universität Stuttgart for recording this spectrum.

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[5] E. Lüddecke, H. Rau, *J. Am. Chem. Soc.*, in press.

Synthesis of Macromolecular Isocyanides with General Solvent Compatibility—Novel Polymer Supports for Solid-Phase Syntheses**

By *Reza Arshady** and *Ivar Ugi*

Polymer-supported reagents and solid-phase techniques have assumed an important role in many areas of chemistry, *e.g.* in the synthesis of peptides and oligonucleotides, as well as in catalysis by enzymes and transition-metal compounds[6].

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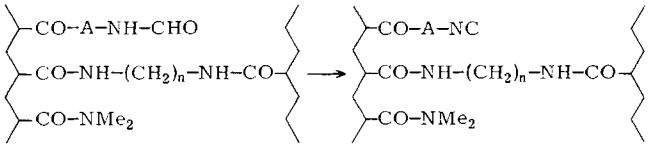
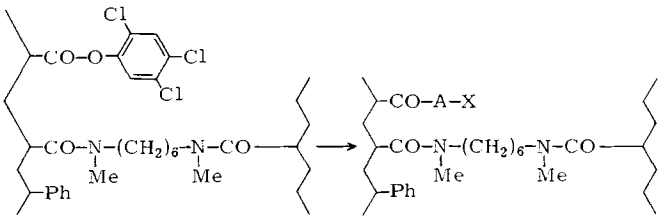
We describe here several novel macromolecular isocyanides of type **2** and **5** (see Table 1).

These polymers afford the combination of the versatile reactivity of the isocyanide group[7a] with the advantages of solid-phase techniques. In contrast to isocyanomethylpolystyrene, our new isocyanide resins have excellent solvent compatibility. The new resins have a swellability of 5—10 mL/g in a wide range of solvents, including water, methanol, dimethylformamide, dichloromethane, benzene, and pyridine.



1 **2**



3

4, X = NH-CHO
5, X = NC

Table 1. Examples of resins of type **2** and **5**.

Resin	n	A—NC	Functionality [mmol/g] [a, b]
2a	1	O—$(CH_2)_3$—NC	1.0
2b	2	O—$(CH_2)_3$—NC	0.6
2c	6	O—$(CH_2)_3$—NC	2.6
2d	1	O—CH_2—$C(Me)_2$—NC	1.9
5a		O—$(CH_2)_6$—NC	3.4
5b		NH—$(CH_2)_2$—C_6H_4—NC(*p*)	3.3 [b]
5c		N(Me)—$(CH_2)_2$—OCO—$(CH_2)_5$—NC	2.8

[a] The data are based on the initial polymer compositions; all of the polymers were subjected to quantitative analysis and showed isocyanide contents of 100 ± 10% of the theoretical values. [b] The isocyanide content of some of the polymers stored at room temperature was found (by IR spectroscopy $\nu(NC) = 2150$ cm^{-1}) to gradually decrease, most rapidly for **5b**, whose isocyanide absorption disappeared completely within 2—3 months.

The macromolecular isocyanides **2** and **5** are obtained by dehydration of the formamides **1** and **4**, respectively. Here, tosyl chloride in pyridine is the reagent of choice[11].

The formamide bead polymers **1**[12] are directly available *via* suspension polymerization, whereas the formamides **4** are derived from the copolymer **3**[13]. The monomers needed for **4** are not compatible as comonomers for suspension polymerizations.

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Synthesis of an all-*cis*-Organocyclotristibane and its Pentacarbonylchromium Complex**

By *Jochen Ellermann** and *Adolf Veit*

Dedicated to Professor Wolfgang Beck on the occasion of his 50th birthday

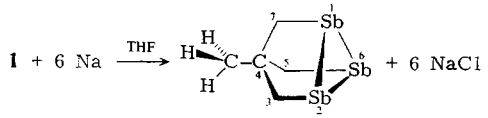
To our knowledge, apart from polymers only two stibanes of general formula $(RSb)_n$[1], the organocyclo*hexa*stibane $(C_6H_5Sb)_6 \cdot C_6H_6$[2a] and the organocyclo*tetra*stibane $(t\text{-}C_4H_9Sb)_4$[2b,c], have so far been reported in the literature. We have now succeeded in synthesizing the first all-*cis*-organocyclo*tri*stibane.

Reaction of tris(dichlorostibane) **1** ($R = C_6H_5$)[3], which is accessible in two steps according to

$$CH_3C(CH_2Br)_3 + 3\,NaSbR_2 \xrightarrow{\text{liq. } NH_3} CH_3C(CH_2SbR_2)_3 + 3\,NaBr$$

$$CH_3C(CH_2SbR_2)_3 + 6\,HCl \xrightarrow{CH_2Cl_2} \underset{\mathbf{1}}{CH_3C(CH_2SbCl_2)_3} + 6\,RH$$

with sodium in tetrahydrofuran (THF), leads to the crystalline 4-methyl-1,2,6-tristibatricyclo[2.2.1.$0^{2,6}$]heptane **2**.



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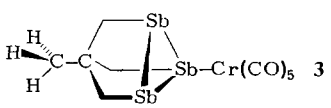
The composition and structure of **2** are confirmed by elemental analysis, osmometric molecular weight determination and by mass spectra (FD, EI)[4].

The cyclotristibane **2**, which is very sensitive to oxidation, is sublimable, readily soluble in THF, moderately soluble in diethyl ether, CH_2Cl_2 and $CHCl_3$, and very sparingly soluble in petroleum ether, methanol, and benzene. Its ^{1}H-NMR spectrum ($CDCl_3$, TMS int.) shows two singlets at $\delta = 1.42$ (CH_2) and 1.65 (CH_3) in the intensity ratio 2:1. The strongest band at 210 cm^{-1} in the Raman spectrum of the solid is assigned to the stretching vibration A_1 of the antimony three-membered ring; the $\nu(Sb_3)$-vibration (E) also to be expected for **2**, assuming C_{3v} molecular symmetry, is assigned by us to the medium-strong Raman band at 151 cm^{-1} [FIR spectrum: 147 (m) cm^{-1}].

$Cr(CO)_5 \cdot THF$, prepared from hexacarbonylchromium(0) by UV irradiation in THF, reacts with **2** in the molar ratio 1:1 to give the complex **3** (molecular symmetry: C_s)[5].



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In the case of η^1-coordination of **2** to $Cr(CO)_5$, $\nu(Sb_3)$(E) in the Raman spectrum at 151 cm^{-1} is split (154 and 140 cm^{-1}, A′ + A″); at the same time a new band appears at 227 cm^{-1}, which we assign to the Cr—Sb stretching vibration.

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Procedure

All operations were carried out under nitrogen and in anhydrous solvents.

2: Granulated sodium (1 g, 43.50 mmol) is added to a stirred solution of **1** (0.73 g, 1.13 mmol) in anhydrous THF (30 mL). The mixture is heated under reflux for 0.5 h, and then cooled. As soon as the solution turns orange in color it is filtered free of excess sodium, undissolved NaCl and decomposition products, and evaporated to dryness. The residue is washed three times with 10 mL of THF and the solvent removed at room temperature *in vacuo*. The crude product can be purified by sublimation (100 °C/0.5 torr): yield 285 mg (61%) **2**, yellow crystals, subl. 216–218 °C.

A stirred solution of $Cr(CO)_6$ (32 mg, 0.145 mmol) in THF (3 mL) is irradiated with UV light for 2 h, and then added dropwise within 5 min to a solution of **2** (63 mg, 0.145 mmol) in THF (15 mL). After 2 h at 20 °C the solvent is removed and the dark-red oily residue is taken up in 4 mL CH_2Cl_2, filtered, and treated with 20 mL petroleum ether. After 2 d at −78 °C, analytically pure **3** separates out; yield 65 mg (72%), dark-red crystals, decomp. 231–234 °C.

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[3] J. Ellermann, A. Veit, unpublished results.

[4] Molecular ion: *m/z* 432, rel. abundance 73%; other fragments observed: 417 ($M - CH_3$; 13%), 377 (CH_2Sb_3; 7%), 363 (Sb_3; 100%), 255 ($CHSb_2$; 2%), 242 (Sb_2; 15%), 190 ($M - Sb_2$; 2%), 175 ($C(CH_2)_3Sb$; 11%), 135 (CH_2Sb; 10%), 121 (Sb; 13%), 69 ($CH_3C(CH_2)_3$; 22%). The mass data are based on ^{121}Sb. The isotopic pattern was as expected.

[5] MS: *m/z* 624 (M^+, 2%), 484 ($M - 5$ CO, successively; 5%), 432 (**2**; 98%), 417 (**2** − CH_3; 8%), 415 (Sb_3Cr; 1%), 363 (Sb_3; 100%); the further fragmentation corresponds to that of **2**. The mass spectral data are based on ^{52}Cr and ^{121}Sb. IR (KBr): 2055, 1980, 1955, 1920; (CH_2Cl_2): 2062, 1995, 1948 cm^{-1} (CO). Raman (solid): 2052, 1974, 1959, 1925, 1908 (CO); 227 (CrSb); 196, 154, 140 cm^{-1} (Sb_3). ^{1}H-NMR ($CDCl_3$, TMS): $\delta = 1.70$ (s, 6H, CH_2), 1.76 (s, 3H, CH_3). The isotopic pattern was as expected.

Stereospecific Synthesis of Palladium(II) Complexes of Macrocyclic Tetradentate Phosphane Ligands**

By *Rainer Bartsch, Sibbele Hietkamp, Stephen Morton,* and *Othmar Stelzer**

As analogs of crown ethers, polydentate macrocyclic phosphanes are of current interest[1–3]. The syntheses previously described require several steps and result in formation of these ligands or their complexes as diastereomeric mixtures in less than satisfactory overall yields. By exploitation of the "template effect" we have now successfully prepared chiral Pd^{II} complexes with tetradentate macrocyclic phosphane ligands in a stereospecific manner in *one* synthetic step.

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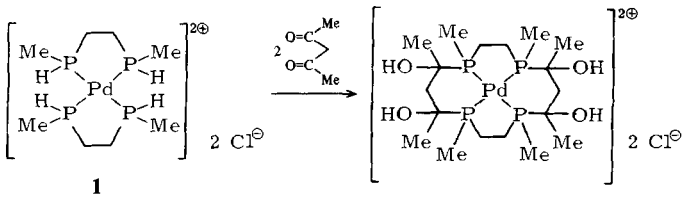
[**] Reactions of Coordinated Ligands, Part 11. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Ministerium für Wissenschaft und Forschung des Landes Nordrhein-Westfalen.—Part 10: R. Bartsch, S. Hietkamp, S. Morton, O. Stelzer, *J. Organomet. Chem. 222* (1981) 263.

The bisphosphane complex **1**—readily accessible from K_2PdCl_4 and $MeHP(CH_2)_2PHMe$—undergoes reaction with two equivalents of acetylacetone in ethanol to form two isomeric cycloadducts **2** and **3** of composition $C_{18}H_{40}Cl_2O_4P_4Pd$. Isomer **2** is only slightly soluble in ethanol, and precipitates out of the reaction mixture. **2** and **3** can be isolated in pure form by recrystallization from water and ethanol/tetrahydrofuran, respectively.



1

2 (20%), **3** (70%)

The novel Pd^{II} complexes **2** and **3** are completely stable in water, and the conductivity of dilute solutions (*ca.* 10^{-4} M) establishes that they are 1:2 electrolytes. Very broad bands at 3180 and 3200 cm^{-1}, respectively, are seen in the IR spectra of **2** and **3**, and these are assigned to OH stretching vibrations. Interestingly, the $^{31}P\{^1H\}$-NMR spectra of each isomer exhibits only a singlet ($\delta = 63.4$ and 60.6, respectively).

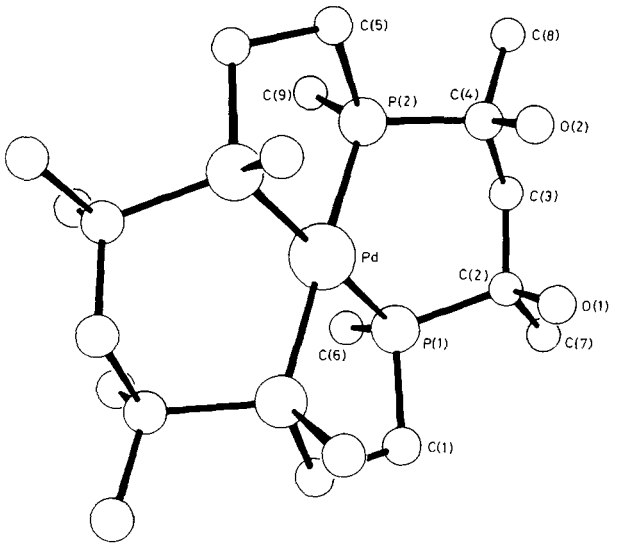


Fig. 1. Structure of the dication of **2** (without H-atoms).

Recrystallization of **2** from water results in isolation of the hydrate $C_{18}H_{40}Cl_2O_4P_4Pd \cdot 4H_2O$. The four P atoms in **2** (Fig. 1) together with the Pd atom form an almost undistorted square-planar arrangement. The *P*-methyl groups are arranged pair-wise in *"cis"* positions. In the chelate six-membered rings, the OH groups are located in axial, and the *C*-methyl groups in equatorial sites. The chelate five-membered rings are in the twist form, and the chelate six-membered rings in the chair form. This also applies to isomer **3**.

Complex **3** has distorted square-pyramidal geometry at the Pd^{II} center (Fig. 2). The Pd atom lies 26 pm above the plane through the four P atoms.

Isomer **2** can be derived from the (*RSSR*)-form and isomer **3** from the (*RSRS*)-form of the starting compound **1**. In aqueous solution the dissociation equilibrium

$$[Pd(L)Cl]^+ \rightleftharpoons [Pd(L)]^{2+} + Cl^-$$

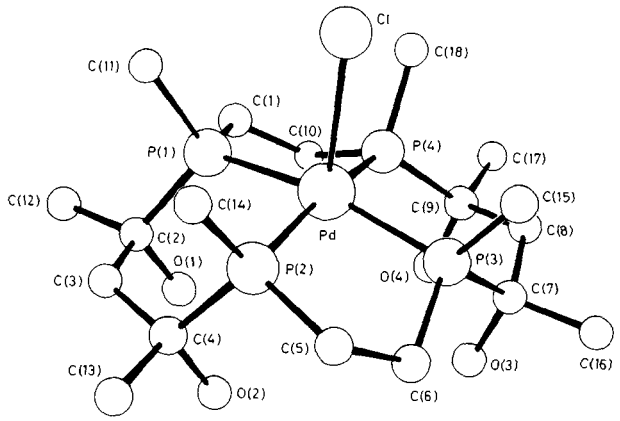


Fig. 2. Structure of the monocation of **3** (without H-atoms).

occurs, as indicated by conductivity measurements (nonlinear $\sqrt{C}/\Lambda_m$ plot). As we have already found for Pd^{II} and Ni^{II} complexes of acyclic chiral tetraphosphaalkanes, this leads to equilibrium of both sides of the surfaces defined by the four P atoms[8]. Therefore, in **2** and **3**, only one $^{31}P\{^1H\}$-NMR signal, respectively, is observed.

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The complete manuscript of this communication appears in: *Angew. Chem. Suppl. 1982*, 807-816

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Triphosphaalkanes $R_2P—CH_2—PR—CH_2—PR_2$ (R = Cl, CH_3)**

By *Sibbele Hietkamp, Herbert Sommer,* and *Othmar Stelzer**

Until now[1] only one example of a tritertiary methylene bridged triphosphaalkane, the 1,1,3,5,5-pentaphenyl-1,3,5-triphosphapentane described by *Appel et al.*[2] was known.

In an investigation of the synthesis of methylenebis(dichlorophosphane) **1** from dichloromethane, trichlorophosphane, and aluminum after *Novikova, Prishchenko,* and *Lutsenko*[3], we have now found that by extraction of the residue (petroleum ether 40/60) after the usual work-up the triphosphapentane **2** can be obtained (*ca.* 16% yield relative to that of **1**). Apart from **2**, the chloromethyl-substituted bisphosphane **3** can be isolated in low yield (*ca.* 8% yield relative to that of **1**).

Products **1** and **3** can be largely separated by distillation (100 °C/0.01 mbar); further purification of **2** by fractional distillation was unsuccessful due to an as yet unexplained decomposition reaction. In contrast, **3** can be isolated in pure form in this way (b.p. = 51 °C/0.15 mbar).

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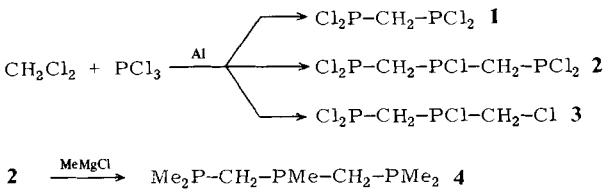

The $^{31}P\{^1H\}$-NMR spectrum of **2** corresponds to the AB_2 type and that of **3** to an AB type (Table 1). When the ^{13}C atoms in **2** are considered in natural abundance, they represent the X part of an ABCX spin system. The $^{13}C\{^1H\}$-NMR spectrum of **3** can be viewed as the superimposition of the X part of an ABX- and the Y part of an ABY-spin system (Table 1).

Table 1. ^{31}P- and ^{13}C-NMR data of compounds **2**, **3**, and **4**.

		2		**3**		**4**
$^{31}P\{^1H\}$-NMR [a]	$\delta_{P(A)}$	84.3	$\delta_{P(A)}$	83.4	$\delta_{P(A)}$	−48.9
	$\delta_{P(B)}$	181.2	$\delta_{P(B)}$	184.2	$\delta_{P(B)}$	−55.8
	J_{AB}	69.4	J_{AB}	63.0	J_{AB}	91.5
$^{13}C\{^1H\}$-NMR [a, b]	$\delta_{C(X)}$	48.6	$\delta_{C(X)}$	53.9	$\delta_{C(Me)}$	16
			$\delta_{C(Y)}$	53.1	$\delta_{C(X)}$	34.7
	$J_{AB}=J_{AC}$	69.4	J_{AB}	63.0	$J_{AB}=J_{AC}$	91.5
	J_{BC}	6.7			J_{BC}	2.8
	J_{AX}	−52.7	J_{AX}	−52.0	J_{AX}	−23.2
			J_{BX}	−60.9		
	J_{BX}	5.1	J_{BY}	5.3	J_{BX}	8.0
	J_{CX}	−62.3	J_{AY}	−44.2	J_{CX}	−22.1

[a] ^{31}P-NMR: H_3PO_4 ext. standard; ^{13}C-NMR: TMS ext. standard; *ca.* 50% solution in C_6D_6; coupling constants in Hz. [b] Labeling of spins: ^{31}P-NMR: **2**, **4** B—C—A—C—B, **3** C—A—C—B; ^{13}C-NMR: **2**, **4** B—C—A—X—C, **3** B—X—A—Y.

Reaction of **2** with methylmagnesium chloride in diethyl ether leads to the permethylated derivative **4**, which can be isolated in pure form (b.p. = 42 °C/0.04 mbar) and characterized by elemental analysis and spectroscopy[6]. The $^{31}P\{^1H\}$-NMR spectrum of **4** also corresponds to the AB_2 type (Table 1). The constitution of the P—C—P—C—P skeleton was verified for the CH_2 groups (X part of an ABCX spin system) by the fine structure of the $^{13}C\{^1H\}$-NMR spectrum.

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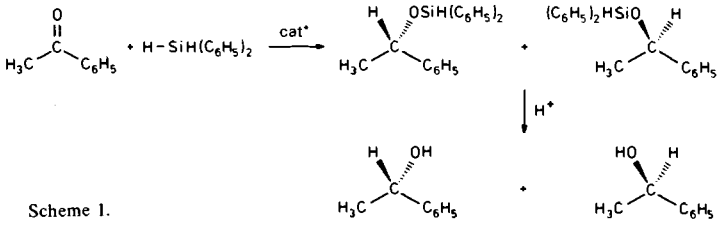
Asymmetric Hydrosilylation of Acetophenone with Rhodium-Complexes of Optically Active Schiff Bases**

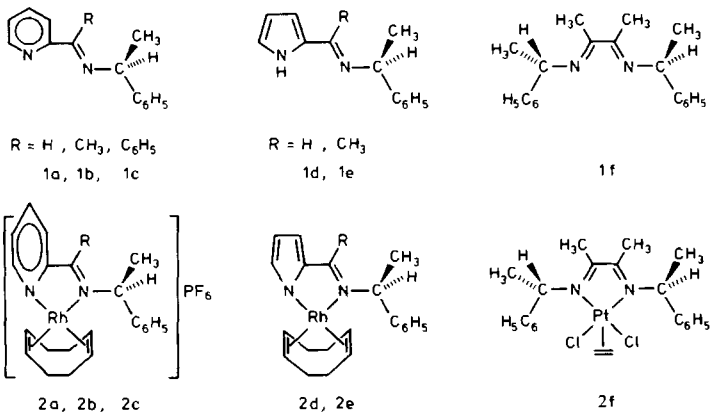
By *Henri Brunner** and *Georg Riepl*

Besides chiral Grignard reagents[1a] and $LiAlH_4$ derivatives[1b], homogeneous catalytic hydrogenations[2] and hydrosilylations[3] with optically active catalysts have been used in recent years for the reduction of prochiral ketones to optically active alcohols. Hitherto, the asymmetric hydrosilylation catalysts, as a rule rhodium or platinum complexes, have without exception contained optically active phosphanes or phosphinites as ligands.



Scheme 1.

We have found that rhodium- and platinum-complexes containing optically active nitrogen ligands are also catalytically active in the model system (Scheme 1) acetophenone/diphenylsilane → 1-phenylethanol[3]. Suitable ligands **1a**—**1f** were obtained by Schiff-base condensation of the corresponding carbonyl compounds with (*S*)-(−)-1-phenylethylamine.



The stoichiometric complexes **2a**—**2f**, though catalytically active, give only slight optical inductions of between 0 and 2% *ee* (Table 1). On the other hand, if the hydrosilylation catalysts are synthesized *in situ* from $[(cod)RhCl]_2$ or $K[PtCl_3(C_2H_4)]H_2O$ with a large excess of ligand, the optical induction increases considerably, in all cases. In the system $[(cod)RhCl]_2$/**1a** with a Rh/ligand ratio of 1 : 13, almost complete hydrosilylation is obtained with an optical induction of 57% *ee*, which surpasses the maximum optical induction of 55% *ee*[4] achieved so far with rhodium complexes of optically active phosphorus ligands on the same model substrate acetophenone/diphenylsilane.

Table 1. Asymmetric hydrosilylation of acetophenone with diphenylsilane (pyridinimine-, pyrrolimine- and diazadiene-noble metal catalysts).

Catalyst system	Rh/ ligand	Rh/ substrate	Reaction time	% Hydrosilylation	% *ee*
2a	1/1	1/320	23 h	38	0.0
2b	1/1	1/380	41 h	35	0.0
2c	1/1	1/350	22 h	59	0.0
2d	1/1	1/340	17 h	70	1.0 (*S*)
2e	1/1	1/320	24 h	57	1.8 (*S*)
2f	1/1	1/400	15 h	10	0.0
$[(cod)RhCl]_2$/**1a**	1/18	1/210	23 h	87	51.1 (*R*)
$[(cod)RhCl]_2$/**1a**	1/13	1/110	41 h	95	57.3 (*R*)
$[(cod)RhCl]_2$/**1b**	1/10	1/210	68 h	66	8.9 (*S*)
$[(cod)RhCl]_2$/**1c**	1/10	1/210	68 h	77	18.3 (*R*)
$K[PtCl_3(C_2H_4)]$/**1f**	1/36	1/300	40 h	74	5.0 (*S*)

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A disadvantage of the Rh/pyridinimine catalysts compared to the Rh/phosphane catalysts is the almost tenfold higher ligand concentration, necessary for generation of the catalytically active species. However, this is no great setback, because the optically active Schiff bases, in contrast to the optically active phosphanes previously used in asymmetric catalysis, are inexpensive and easy to prepare. Considering that the components of the Schiff bases **1a**—**1f** and similar compounds—carbonyl compound and optically active primary amine—are variable within very wide limits, there is an almost inexhaustible potential for new catalysts.

A striking feature of the results in Table 1 is the surprising effect of various groups R in the pyridinimine series. In the case of **1a** (R = H), the (*R*)-configuration predominates (57%) in the resulting 1-phenylethanol, whereas in the case of **1b** ($R=CH_3$), the (*S*)-configuration (9%) predominates, and for **1c** ($R=C_6H_5$) the (*R*)-configuration is once again predominant (18%), though all three Schiff bases derive from (*S*)-(−)-1-phenylethylamine. This confirms the dominating role of the substituents R on the azomethine C-atom regarding the arrangement of the optically active group on the neighboring N-atom, which had already manifested itself in the optical induction of the metal configuration[5] and which obviously also exerts a decisive influence on the configuration of the product in asymmetric hydrosilylations.

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Preparation of a Graphite Fluoride Film on Aluminum

By *Hiroaki Yamada, Tsuyoshi Nakajima,* and *Nobuatsu Watanabe**

When a mixture of sheet aluminum and graphite fluoride powder $[(CF)_n]$[1,2,5] is heated at 450–600 °C in F_2 (0.1–1.0 bar) a graphite fluoride film is formed on the surface of the aluminum. This film can be prepared more conveniently by allowing aluminum metal to react with natural graphite powder (1 bar F_2, 600 °C).

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X-ray microanalysis showed that the film contained almost 50% fluorine and 30% carbon, but almost no oxygen. X-ray diffraction studies indicated the absence of aluminum oxide, but that both α- and γ-aluminum fluoride were present[10].

The ESCA spectra of the film yield C1s and F1s binding energies (E_B) of 290.0 ± 0.2 and 689.0 ± 0.2 eV, respectively, which were assigned to graphite fluoride[9] $[(CF)_n]$ (Fig. 2A).

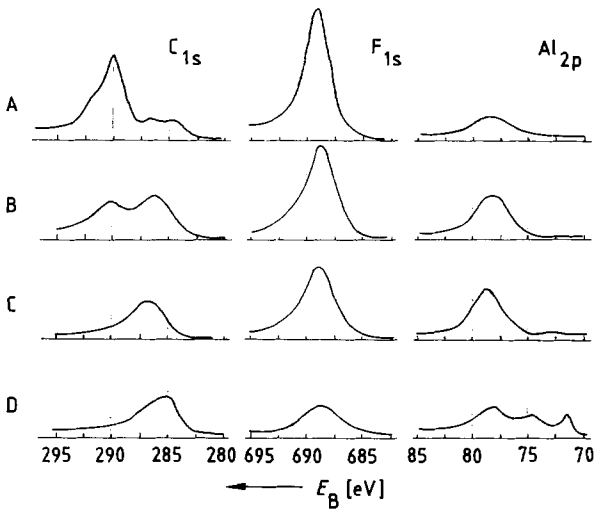

Fig. 2. ESCA spectra of the graphite fluoride film on aluminum obtained by heating aluminum with graphite fluoride under F_2 (450 °C, 1 bar F_2, 48 h), $Mg_{K\alpha}$ radiation. A) Film surface; B)–D) after successive polishing of the surface with sandpaper. E_B = binding energy. Standard: contaminating carbon, E_B (C1s) = 285.0 eV.

The peak for Al2p binding energy located at 78.5 ± 0.2 eV suggests that the aluminum atom is bonded to fluorine or to a fluorocarbon. Removal of the surface layer from the film resulted in a rapid decrease in the C1s maximum at 290 eV and an increase in that at 286.5 ± 0.2 eV (Fig. 2B–D). The latter maximum is characteristic of this film and its chemical shift is assigned to a carbon atom of part structure Al—C—F.

The film is gray to grayish black in color and has a smooth lustrous surface; it could not be detached mechanically from the aluminum support. The thickness of the film is about 3 μm. The contact angle of distilled water on the film is 120°, and the specific resistance is greater than $4\times10^{10}\ \Omega\cdot$cm at room temperature. In addition, the film has high corrosion-resistance to acidic and alkaline solutions, and its thermal decomposition temperature is 600 °C in air.

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CAS Registry numbers:
Al, 7429-90-5; graphite fluoride, 11113-63-6

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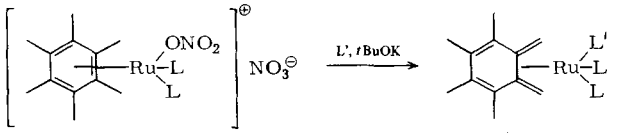
Reversible Double Deprotonation of Hexamethylbenzene on Ruthenium: Formation of a Fluxional η^3-Benzyl Compound by Protonation of an *o*-Quinodimethane Complex of Ruthenium(0)

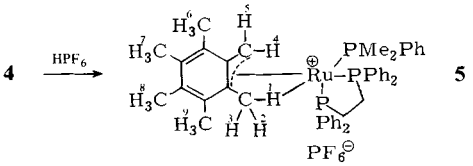
By *Martin A. Bennett**, *Ian J. McMahon*, and *Terence W. Turney*

Ruthenium(0) complexes **1**—**4** containing 1,2,3,4-tetramethyl-5,6-bis(methylene)-1,3-cyclohexadiene (*o*-quinodimethane) are formed by abstraction of two protons from a η^6-hexamethylbenzeneruthenium(II) complex, the metal atom being coordinated to the exocyclic diene.



1, L = L' = $P(OMe)_3$
2, L = L' = $P(OCH_2)_3CMe$
3, L = L' = PMe_2Ph
4, L_2 = diphos; L' = PMe_2Ph

The double deprotonation is reversible: complex **1** reacts with an excess of HBF_4 or HPF_6 to give $[Ru\{P(OMe)_3\}_3(\eta\text{-}C_6Me_6)]X_2$ and there is NMR spectroscopic evidence for a mono-protonated intermediate when a deficiency of acid is employed at 0 °C. In contrast, **4** reacts even with an excess of 60% aqueous HPF_6 to give a yellow, air-stable, monoprotonated salt **5**.



The cation **5** is formulated as a fluxional η^3-benzyl complex in which the added proton bridges the metal atom and a methyl carbon atom[14, 15]. Exchange between this proton (H^1) and the two protons H^2, H^3 on the carbon atom is rapid on the NMR time scale, even at −90 °C [^{1}H-NMR (CD_2Cl_2, −30 °C): δ = −2.31 (m, $H^{1,2,3}$), 1.42, 1.58, 2.17 (s, s, s, each 3H, $H^{6,7,9}$), 2.40 (s, 3H^8), 3.17 (m, H^5), *etc.*]. Above −30 °C a $\eta^3 \rightleftharpoons \eta^1$ benzyl interconversion[16, 17] takes place which interchanges $H^{1,2,3}$ with H^6, and H^7 with H^9, but leaves H^8 unaffected. In the range 28—80 °C all the ring methyl protons begin to become equivalent, probably owing to successive C—H cleavages and formation of Ru—H bonds (cf. $Mn(CO)_3(\eta^3\text{-}C_6H_9)$[14]), which allow the $L_2L'Ru$ group to traverse the substituents on the six-membered ring.

The formation of **5** from **4** is clearly analogous to the generation of η^3-allyliron(II) complexes by protonation of $FeL_3(\eta^4$-diene) compounds[9], and supports the formulation of **1**—**4** as η^4-dieneruthenium(0) in preference to the alternative α,α'-*o*-xylenediylruthenium(II) complexes.

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(1), 81408-64-2; *(2)*, 81408-65-3; *(3)*, 81408-66-4; *(4)*, 81408-67-5; *(5)*, 81408-69-7; $[Ru(ONO_2)(P(OMe)_3)_2(\eta\text{-}C_6Me_6)]NO_3$, 81408-71-1; $[Ru(ONO_2)(P(OCH_2)_3CMe)_2(\eta\text{-}C_6Me_6)]NO_3$, 81408-73-3; $[Ru(ONO_2)(PMe_2Ph)_2(\eta\text{-}C_6Me_6)]NO_3$, 81408-75-5; $[Ru(ONO_2)(diphos)(\eta\text{-}C_6Me_6)]NO_3$, 81408-77-7; $[Ru\{P(OMe)_3\}_3(\eta\text{-}C_6Me_6)]^{2+}$, 81408-78-8

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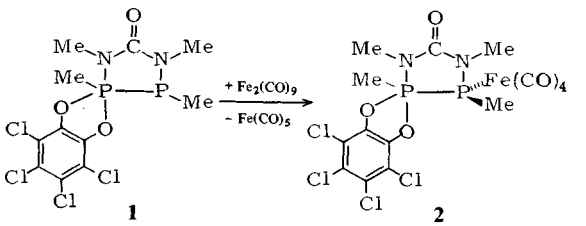
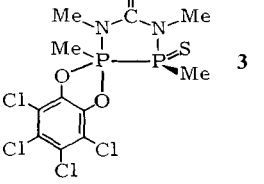
Synthesis and Structure of the First Transition Metal Complex of a Phosphorus Compound with a Direct λ^3P—λ^5P Bond

By *John W. Gilje*, *William S. Sheldrick*, *Norbert Weferling*, and *Reinhard Schmutzler**

Although many complexes of triply coordinated phosphorus with transition metals have been known for some time, there are few cases involving λ^3P-λ^3P diphosphane ligands, and only one example of a complex in which the free ligand contains a λ^4P-λ^3P structural unit is known[3]. We have now studied the donor properties of the λ^5P-λ^3P diphosphorus compound **1**, which we had previously prepared[4]. The first representatives of this novel class of compounds were only recently synthesized and structurally characterized[5]. Reaction of an equimolar amount of **1** with $Fe_2(CO)_9$ affords, quantitatively, the tetracarbonyliron complex **2** (Fig. 1), which is stable towards atmospheric oxygen and moisture.





An X-ray structure analysis of **2** indicated that this unusual molecule contains both a pentacoordinated metal (Fe) as well as a pentacoordinated nonmetal (P2). The iron atom has trigonal bipyramidal coordination, while the coordination at P2 is largely square pyramidal.

Both angles O1P2P1 and O2P2N2 (150.8(1) and 151.7(1)°, respectively) closely approach that expected for

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a square pyramid (150°). The difference in the P201 (169.8(3) pm) and P202 (173.5(2) pm) bond lengths, however, indicate that P2 exhibits some residual trigonal-bipyramidal character. Analysis of the interplanar dihedral angles for the normalized bond lengths shows that in **2** P2

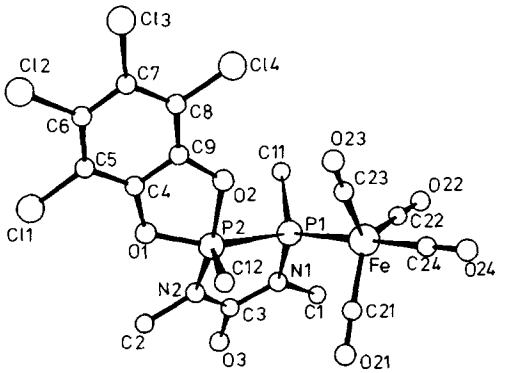

Fig. 1. Molecular structure of **2** in the crystal. Details of the crystal structure can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen (F.R.G.) by quoting the number CSD 50 175, the name of the author, and the complete citation of the article.

has more than 80% square pyramidal character. In contrast, **3** exhibits only *ca.* 56% C_{2v} distortion towards this geometry[9]. The SP1P2 angle in **3** (112.8(1)°) is considerably smaller than the FeP1P2 angle in **2** (120.3(1)°). Possibly the different coordination at P2 in **2** and **3** has its origin in steric interactions *e.g.* between C12 and atoms of the $Fe(CO)_4$ group. The P1P2 distance (224.5(1) pm) in **2** is in the expected range (218—225 pm). In both **2** and **3** the two methyl groups C11 and C12 have *trans*-orientations; a *cis* arrangement would be sterically much less favorable.

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Cu-H_2 Photochemistry in the Matrix; ESR, FTIR, UV/VIS Spectroscopic and Kinetic Studies**

By *Geoffrey A. Ozin**, *Steven A. Mitchell*, and *Jamie García Prieto*

In this communication we wish to report that photoexcited copper atoms react with molecular hydrogen in a krypton matrix to yield CuH and H atoms.

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The UV/VIS spectrum of Cu atoms isolated in a Kr/H_2 matrix at 12 K ($Cu:Kr:H_2 = 1:10^4:10^3$) closely resembled that observed for Cu atoms in a pure Kr matrix[7], although the effects caused by 310 nm photoexcitation of the entrapped Cu atoms ($4^2P \leftarrow 4^2S$) were markedly different. Whereas in the case of the pure Kr matrix loss of Cu atoms was characterized by approximately second order kinetics, consistent with the bimolecular dimerization $2Cu \rightarrow Cu_2$, the photoinduced decay of Cu atoms in the Kr/H_2 matrix was much faster, and was characterized by first order kinetics; such decay kinetics would be expected for a reaction of the type $Cu + H_2 \rightarrow$ products, where H_2 is in great excess. Only minimal growth of Cu_2 was observed under the conditions mentioned. Furthermore, the photodecay rates of Cu atoms in Kr/H_2 and Kr/D_2 matrices were found to be identical.

Direct evidence for a chemical reaction involving photoexcited copper atoms and molecular hydrogen was obtained by means of *in situ* ESR and FTIR studies of $Cu/Kr/H_2$ matrices[8].

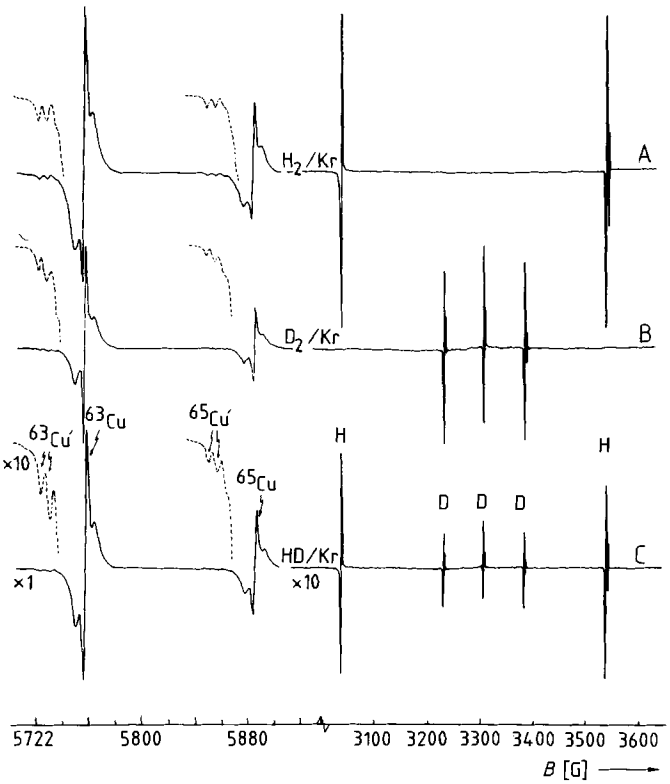

Fig. 1. Left: Part of the ESR spectra (Varian E4, 9.278 GHz) showing the high field doublet associated with ^{65}Cu and ^{63}Cu atoms isolated in freshly deposited Cu-containing Kr/H_2 (A), Kr/D_2 (B), and Kr/HD (C) matrices (ratios $1:10^4:10^3$) at 12 K. Right: Spectra showing the presence of H and D atoms in the various matrices after ≃ 1 h photolysis at 310 nm. No H or D atoms were detected prior to photolysis.

In each case the ESR spectra of the $Cu/Kr/H_2$, $Cu/Kr/D_2$, and Cu/Kr/HD matrices showed only the known[9a] spectrum of Cu atoms, and no H or D atoms. The high field doublet associated with ^{63}Cu and ^{65}Cu atoms is reproduced in Figure 1. Photoexcitation (310 nm) of the entrapped Cu atoms caused decay of their resonance lines with concurrent appearance and rapid growth of resonance lines due to H and/or D atoms (Fig. 1, right). No lines attributable to Cu^{II} species, *e.g.* CuH_2 were observed in these experiments in contrast to similar studies with CH_4[1] and C_2H_6[5] in which the primary products H_3CCuH and H_5C_2CuH, respectively, were detected in addition to

the major secondary photolysis channel $^{\circ}CH_3 + CuH$ and $^{\circ}C_2H_5 + CuH$, respectively. Interestingly, in Kr/HD matrices there was a pronounced intramolecular isotope effect and H atoms were approximately twice as favored over D atoms. This isotope effect and the identical copper atom photodecay rates in Kr/H_2 and Kr/D_2 matrices are similar in both direction and magnitude to those found for the reactions of $^3P_{0,1}$-Cd and -Hg atoms with HD, H_2, and D_2 in the gas phase. These reactions are known to produce the metal hydride, H, and D atoms, respectively, and have been postulated to occur by a direct insertion-dissociation mechanism involving side-on attack of H_2 or D_2 by the excited metal atom. However, to make definitive statements on the Cu/H_2 system, further experiments are necessary.

The formation of CuH and CuD, respectively, as products of the photochemical reaction of Cu atoms in a Kr/H_2, Kr/D_2 or Kr/HD matrix was detected by FTIR studies [intense bands in the IR spectra at 1852 ($Cu/Kr/H_2$) and 1336 cm^{-1} ($Cu/Kr/D_2$)][13].

An interesting possibility is that the much less intense band at 1907 ($Cu/Kr/H_2$) or 1388 cm^{-1} ($Cu/Kr/D_2$), respectively, is associated with a dicopper monohydride species, formed by a reaction of the type $Cu + CuH \rightarrow Cu_2H$.

In summary, the photochemical reaction of copper atoms with molecular hydrogen in Kr matrices can be written as follows:

$$Cu + H_2 \xrightarrow[\text{Kr matrix, 12 K}]{\text{UV/310 nm}} CuH + H$$

We found no evidence for formation of a copper dihydride HCuH intermediate.

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CH_4 Activation by Photoexcited Cu_2 Molecules**

By *Geoffrey A. Ozin**, *Steven A. Mitchell*, and *Jamie García-Prieto*

We report here our observations concerning the first example of alkane activation using a selectively photoexcited M_2 species: the matrix reaction of Cu_2(B) with CH_4.

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Evidence for this photochemical reaction stem from a number of sources, including UV/VIS absorption, fluorescence emission/excitation and ESR spectroscopy. In a typical UV/VIS absorption trace of a Cu/CH_4 matrix ($1:10^3$, 12 K) the freshly desposited sample shows the presence of Cu atoms which coexist with small amounts of Cu_2. Prolonged resonance excitation of the Cu atoms [15 minutes, 320 nm intensity at the sample: 80 μwatt cm^{-2}; $Cu(^2P) \leftarrow Cu(^2S)$] causes rapid bleaching of all the Cu atom absorptions, and formation of $^{\circ}CH_3$ and CuH as the major photoproducts (absorbing at $\lambda = 200-250$ nm) with very little alteration of the concentration of Cu_2 (Fig. 1)[1].

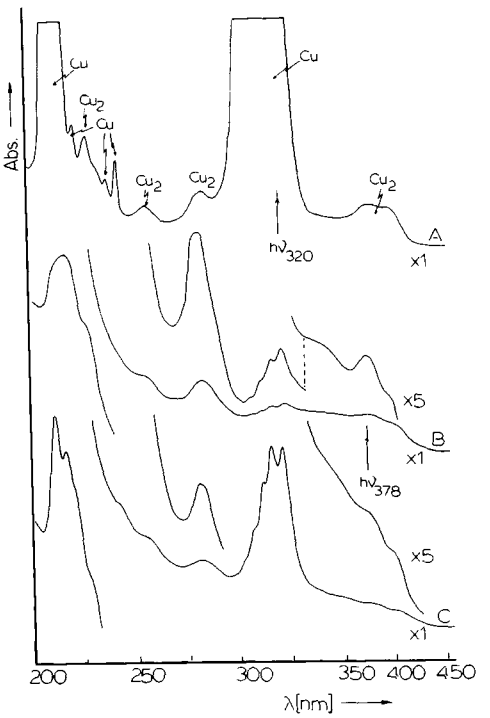

Fig. 1. UV/VIS absorption spectrum of Cu atoms in a CH_4 matrix ($Cu:CH_4 \approx 1:10^3$) at 12 K. A) Directly after deposition, B) after irradiation for 15 min at 320 nm, and C) after irradiation for 5 min at 378 nm (cf. text).

Subsequent photoexcitation of Cu_2 (5 min, $\lambda = 378$ nm) results in rapid bleaching of the Cu_2 absorptions, with concurrent ten-fold growth in the intensity of the Cu atom resonance absorption bands. This observation should be sharply contrasted with the minor net photodissociative yield (10% after 30 min) following similar photoexcitation of Cu_2 in rare gas matrices[7]. Furthermore, the $Cu(^2D) \rightarrow Cu(^2S)$ emission observed in rare gas matrices after photoexcitation of Cu_2 is completely quenched in the corresponding spectra of CH_4 matrices[5]. ESR spectroscopy clearly revealed significant production of $^{\circ}CH_3$ radicals (quartet centered around $g = 2$) following excitation of Cu_2 in CH_4. Trace amounts of H atoms (doublet centered around $g = 2$) were observed in these experiments; however, no evidence for the insertion product H_3CCuH was obtained, although because of the low Cu_2 concentration employed in these experiments the amount of H_3CCuH could have been below the detection limit of the ESR measurements. This observation should be contrasted with the reaction of $Cu(^2P)$ formed by directed resonance excitation of $Cu(^2S)$ with CH_4 in the matrix, which leads to efficient generation of H_3CCuH in the primary step[1].

These results point to very efficient photodissociation of Cu_2 excited in CH_4 matrices; this appears to have its origin in the chemical quenching of the $Cu(^2D)$ photofragment:

$$Cu(^2D) + CH_4 \rightarrow {}^{\ominus}CH_3 + CuH$$

This eliminates the competing cage-assisted recombination pathway which predominates in rare gas matrices[5,7]. This proposal is entirely consistent with our observation of a large, net Cu_2 photodissociative yield of the immobilized ground state [$Cu(^2S)$] of Cu atoms, which occurs in addition to the excited state [$Cu(^2D)$].

These results may be significant as they point to the possibility of excited state selectivity in the condensed phase photosensitization reactions of Cu atoms with CH_4:

$$Cu(^2P) + CH_4 \xrightarrow{\text{insertion}} H_3CCuH$$

$$Cu(^2D) + CH_4 \xrightarrow{\text{abstraction}} H_3C^{\ominus} + CuH$$

$$Cu(^2S) + CH_4 \xrightarrow{\text{no reaction}} Cu + CH_4$$

In conclusion, photochemistry of metal atoms and dimetal species opens up the possibility of activating saturated hydrocarbons and performing selective alkane transformations[1,3]; in this connection certain M_2 species can be photoexcited with visible light.

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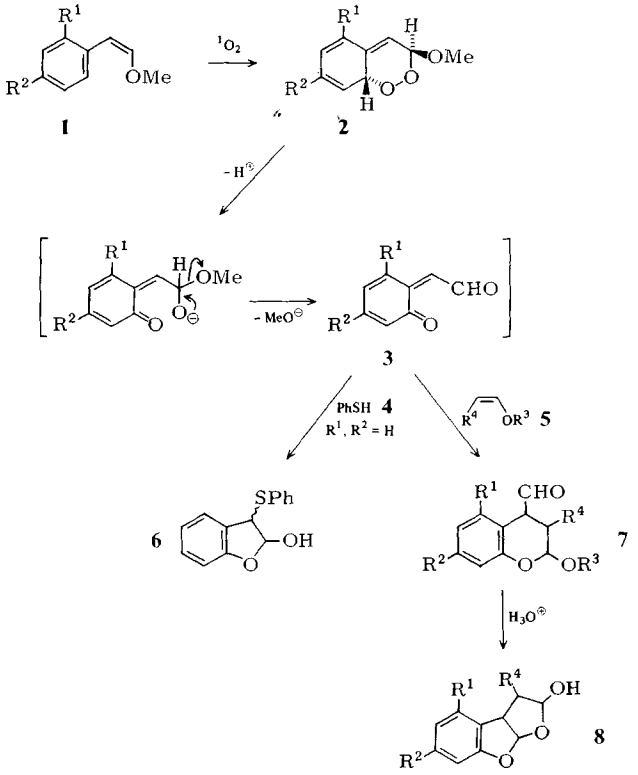
o-Benzoquinone Monoformylmethides by Sensitized Photooxygenation of *cis*-β-Methoxystyrenes

By *Masakatsu Matsumoto* and *Keiko Kuroda**

A reactive *o*-quinone methide[1] is often generated as a reaction intermediate by dehydration[2] or by pyrolysis[3] at high temperature. Mainly because of these forcing conditions, generation of quinone methides possessing labile functional groups has hardly been attempted so far. We report here an effective generation of new *o*-quinone methides **3**, which have a formyl group at the exocyclic carbon, from cyclic peroxides **2** of cis-β-methoxystyrenes **1** under mild conditions. These quinone derivatives **3** react with enol ethers **5** affording 4-formylchromans **7**, which are utilized as versatile intermediates in the synthesis of furobenzofuran-type mycotoxins.

Sensitized photooxygenation of *cis*-β-methoxystyrene **1a** at low temperature gives quantitatively an unstable 1,4-endoperoxide **2a**[4a], which decomposes into a complex mixture at room temperature[4b,c]. However, decomposition of



1	R^1	R^2	5	R^3	R^4	7
1a	H	H	+ **5a**	*i*Bu	H	→ **7a**
1a	H	H	+ **5b**	—CH_2CH_2—		→ **7b**
1a	H	H	+ **5c**	Me	Ph	→ **7c**
1b	H	MeO	+ **5a**	*i*Bu	H	→ **7d**
1c	$PhCH_2O$	MeO	+ **5a**	*i*Bu	H	→ **7e**

2a was found to proceed cleanly in the presence of excess isobutyl vinyl ether **5a**; chromatographic purification of the reaction mixture afforded a 4-formylchroman **7a** in 68% yield[5]. In this reaction, the peroxide **2a** is believed to decompose initially into the quinone methide **3a** and methanol. Diels-Alder addition of **3a** to **5a** then leads to the product **7a**. Intermediary **3a** was further confirmed by reaction of **2a** with a nucleophile such as thiophenol **4**, which affords a stereoisomeric mixture of lactols **6** in 45% yield.

The addition of **3a** to 2,3-dihydrofuran **5b** and *cis*-β-methoxystyrene **1a** (≡ **5c**), respectively, afforded the 4-formylchromans **7b** (13%) and **7c** (54%). Ring-substituted *cis*-β-methoxystyrenes **1b** and **1c** gave the chromans **7d** (29%) and **7e** (39%), respectively, when allowed to react with **5a**. On the other hand, reaction of the peroxide from the *trans*-isomer of **1a** with vinyl ethers gave unfavorable results.

The formylchromans **7** are useful synthetic intermediates. For example, under acid catalysis with H_2SO_4 they give furobenzofurans **8**. The reaction sequence described here is suitable for the synthesis of some mycotoxins possessing a furobenzofuran skeleton such as sterigmatocystin and aflatoxins[4d].

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[5] **7a**: A solution of *cis*-β-methoxystyrene **1a** (0.67 g, 5 mmol) and tetraphenylporphyrine (5 mg) in CH_2Cl_2 (20 mL) was irradiated with visible light under O_2 at −78 °C until an equimolar amount of oxygen was consumed (*ca.* 4 h). Isobutyl vinyl ether **5a** (5 g) was added to the mixture which was allowed to stand for 15 h at 5 °C. The reaction mixture was condensed *in vacuo* and chromatographed on SiO_2 (Wako C-200). Elution with CH_2Cl_2 gave **7a** [747 mg, 68% yield based on the consumed **1a**]; b.p. *100 °C/0.24* torr; ^{1}H-NMR (CCl_4): δ = 0.78 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H), 1.52–2.00 (m, 1H), 2.00–2.20 (m, 2H), 3.12–3.60 (m, 2H), 3.57–3.80 (m, 1H), 5.05–5.16 (m, 1H), 6.66–7.18 (m, 4H), 9.56 (d, J = 3.5 Hz, 1H).

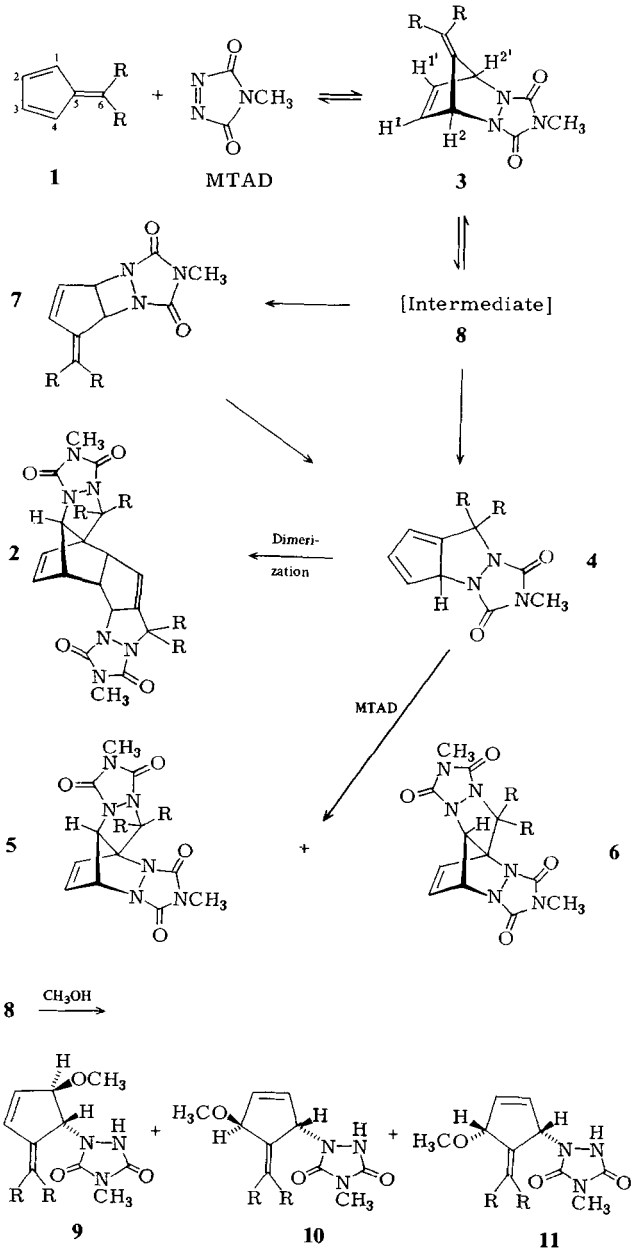
Reaction of 4-Methyl-1,2,4-triazoline-3,5-dione with Fulvenes: A 1,3-Sigmatropic Shift involving a Dipolar Intermediate**

By *Henrik Olsen**

The Diels-Alder reaction of azodicarbonyl compounds and fulvenes has led to a wide variety of polycyclic *N*-heterocycles. We have now found that the reaction between 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) and fulvenes **1a** and **1b** provides novel products, the heptacycles **2a** and **2b**, respectively, formally derived by successive [6+2]- and [4+2]-cycloadditions. Since a $[_\pi 6_s + _\pi 2_s]$-cycloaddition contravenes the Woodward-Hoffmann rules, the mechanistic details of this reaction were examined more closely.

Surprisingly, the reaction between **1a** and MTAD at room temperature did not furnish the expected Diels-Alder adduct **3a**. The ^{1}H-NMR spectrum of the isolated product (72% yield) is in complete agreement with the structure of the *bis*-adduct **2a**. In addition to six singlets for the methyl groups (δ = 3.00, 2.98, 1.78, 1.65, 1.44, 1.41) eight groups of signals for the eight other protons are observed. On the other hand, reaction of MTAD and **1b** under analogous conditions furnished *bis*-adduct **2b** (86% yield). Formation of heptacycles **2** strongly suggests that MTAD reacts initially with **1** to give the 1,6-addition products **4**. When the cycloaddition reaction between **1a** and **1b** and MTAD was performed (in the ratio 1:2) the 1:2 adducts **5a** (49%) and **6a** (36%) or **5b** (88%), respectively, could be isolated. Clearly the Diels-Alder reaction of **4a** and **4b** with MTAD must be considerably faster than the dimerization.

In order to establish whether the pathway leading to **4** from **1** and MTAD could proceed *via* initial [4+2]-cycloaddition followed by a formal [1,3]-sigmatropic shift or directly *via* a [6+2]-cycloaddition, MTAD was added to a CD_2Cl_2 solution of dimethylfulvene **1a** (1:1) in an NMR tube at −78 °C. ^{1}H- [(100 MHz), δ = 6.57 (AA′ part of an AA′XX′ system, 1- and 1′-H), 5.41 (XX′ part, 2- and 2′-H), 2.94 (s, NCH_3), 1.72 (s, CH_3)] and ^{13}C-NMR spectra indicate that the [4+2]-cycloadduct **3a** is formed initially.



a, R = Me; **b**, R = Ph

Scheme 1.

At −10 °C **3a** rearranged to afford isomers **4a** and **7a**. In the final stages of the reaction only signals corresponding to **2a**, **5a**, **6a**, and **1a** could be observed. Similarly, the reaction between **1b** and MTAD at −78 °C furnished **3b**, *which rearranged at −10 °C to furnish* **2b**.

In preliminary investigations of the mechanism (concerted, diradical, or zwitterionic), remarkably low-energy barriers for the conversion **3b**→**4b** (ΔH^{+} = 21.7 ± .2 kcal/mol, ΔS^{+} = 6.5 ± .6 cal/mol K in [D_8]THF) were estimated. Evidence for a true intermediate on the potential energy surface was provided by performing the cycloaddition reaction between **1b** and MTAD in CH_2Cl_2/MeOH (1:5) at −45 °C. NMR spectroscopy (at −45 °C) indicates the initial formation of **3b**; however, warming the solution to room temperature results in the formation of the metha-

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nol adducts **9b**, **10b**, and **11b**, consistent with the intervention of intermediate **8**, which has a zwitterion-like character[17]. However, since the rate of transformation **3b**→**4b** is by and large insensitive to solvent polarity ($k_{CD_3CN}/k_{[D_8]THF}=2.2$), the intermediate has to be mediated on the continuous scale between biradical and zwitterion[21]. We consider **8** to be a resonance hybrid of zwitterion and biradical mesomeric structures[23].

The interrelationship of the various adducts is depicted in Scheme 1. One possibility is that **8** may collapse to produce both **7** and **4**. The former (**7**) would then have to rearrange subsequently to **4**, either by a concerted [1,5]-sigmatropic shift or by a stepwise process. Alternatively, formation of **4** could result from **7** and not directly from **8**. This is in accord with the reported behavior of the [2+4]-cycloadduct between tetracyanoethylene and dicyclopropylfulvene, which consecutively forms [2+2]- and [2+6]-cycloadducts *via* zwitterionic intermediates[22]. Since in the NMR study of the reaction of **1a** with MTAD the signals of **1a**, **5a**, and **6a** remained constant with respect to an internal standard as soon as **3a** had disappeared from the reaction mixture, the existence of an equilibrium **1** + MTAD⇄**3** is supported; an analogous equilibrium has also been reported in the literature[26]. An alternative would be dissociation of intermediate **8** into **1** and MTAD.

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Metallacyclosulfanes: Synthesis of Bis(pentamethylcyclopentadienyl)titana(IV)cyclotetrasulfane**

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Since the report of the complex $(C_5H_5)_2TiS_5$[1a], a number of metallacyclosulfanes *i.e.* compounds containing an MS_x ring have been prepared[1b]. Except for the special case of disulfide complexes only rings with x = 4 or 5 have been characterized. Recently, we prepared the complexes $(C_5H_5)_2ME_5$ (M = Zr, Hf and E = S, Se) and compared the ring flipping activation energies of the pentasulfides to that reported for $(C_5H_5)_2TiS_5$[2a]. Here we report that attempted preparation of the analogous pentamethylcyclopentadienyl complexes led to the isolation of the first confirmed examples of metallacyclotetrasulfanes $(Me_5C_5)_2MS_3$, M = Ti, Zr[2b].

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In the solid state the TiS_3 ring in $(Me_5C_5)_2TiS_3$ is nonplanar, with S(2) being significantly displaced in the direction of one Me_5C_5 ring (pseudoaxial). The dihedral angle between the two planes formed by atoms TiS(1)S(2) and S(1)S(2)S(3) is 49°. The Ti—S(2) distance (2.77 Å) seems short but it would only lengthen to about 3.0 Å if the ring were planar. Thus, it is not possible to rule out a substantial interaction between Ti and S(2)[3a] (for further information see Fig. 1).

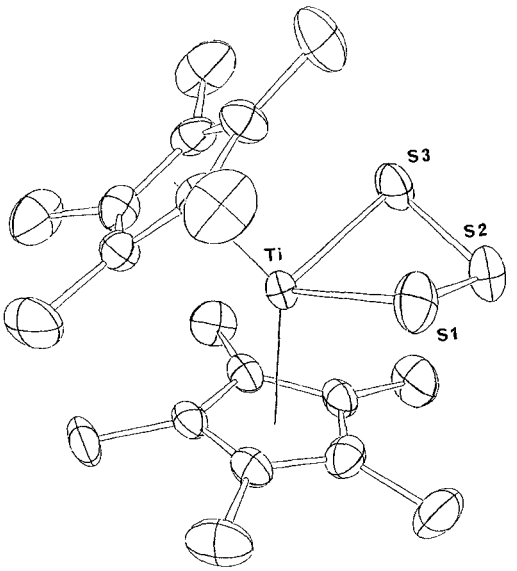

Fig. 1. Structure of $(Me_5C_5)_2TiS_3$ in the crystal (ORTEP representation, methyl protons omitted). $P2_1/c$, $a=8.770(8)$, $b=13.885(6)$, $c=17.20(1)$ Å, $\beta=103.75(6)°$. Single crystal diffractometer (Picker FACS-1, software from National Research Council of Canada), $Mo_{K\alpha}$ irradiation, graphite monochromator, θ-2θ scan, $3.5° < 2\theta < 45°$, 1829 reflections with $I > 3\sigma(I)$, direct methods, R = 5.8%. Most important bond lengths [Å] and angles [°] (averaged where appropriate; values in square brackets apply to $(C_5H_5)_2TiS_5$ [3b]): TiS 2.413(4), SS 2.041(5), $(Me_5C_5)Ti(Me_5C_5)$ 136.85(3) [$(C_5H_5)Ti(C_5H_5)$ 133.7], STiS 84.44(9) [94.6], TiSS 76.34(1) [108.00(8)], SSS 105.3(1) [104.9(1)].

Both $(Me_5C_5)_2TiS_3$ and $(Me_5C_5)_2ZrS_3$ exhibit variable temperature ^{1}H-NMR spectra. At room temperature one peak is observed for the methyl protons. Upon cooling this peak broadens, collapses (−80 to −90 °C) and reappears as two peaks (overlapping for Ti, resolved for Zr) which continue to sharpen until at lower temperatures they also broaden, collapse and in the case of the Ti complex begin to reappear as a number of small peaks (< −105 °C). The changes at higher temperatures are assigned to the slowing of ring reorientation ("ring-flipping"[4]) until the peaks due to the Me_5C_5 protons in the pseudoaxial and equatorial environments are resolved. We feel that the low temperature changes are due to the slowing of the Me_5C_5 ring rotation about the ring-metal axis. The barriers to "ring-flipping" are 40 ± 2 kJ mol^{-1} for both complexes. These values are smaller than those for the pentasulfides, and within the latter series the TiS_5 ring has a much higher barrier than its congeners.

The "natural" ring size for the metallacyclosulfanes of the $(C_5H_5)_2M$ system, where M is a group IVa metal, is six. Apparently, the ring size for the $(Me_5C_5)_2M$ system is four, even in the presence of excess sulfur.

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[1] a) H. Köpf, B. Block, M. Schmidt, *Chem. Ber. 101* (1968) 272; b) see M. Schmidt, G. G. Hoffmann, *Z. Naturforsch. B 34* (1979) 451, and references cited therein.

[2] a) J. M. McCall, A. Shaver, *J. Organometal. Chem. 193* (1980) C37, and unpublished results; b) $(Me_5C_5)_2TiCl_2$ [5] (0.388 g) in dry, O_2-free tetrahydrofuran (THF) was added dropwise to a THF solution of sulfur (molar ratio 1:3/8 S_8) and Li_2S_2. The solution was stirred under nitrogen for 1 h at room temperature and refluxed for a further 10.5 h. The solvent was removed *in vacuo* and the residue extracted with 2 × 25 ml of CH_2Cl_2. The solution was filtered and evaporated to dryness *in vacuo* to give a deep purple microcrystalline solid which was recrystallized from THF/pentane to afford black crystals (55%; m.p. 149–152°).

[3] a) An unsymmetrical bonding mode has been observed for the allyl ligand in $(C_5H_5)_2TiC_5H_9$; see R. B. Helmholdt, F. Jellinek, H. A. Martin, A. Vos, *Recl. Trav. Chim. Pays-Bas 86* (1967) 1263; b) E. F. Epstein, I. Bernal, *J. Organometal. Chem. 26* (1971) 229.

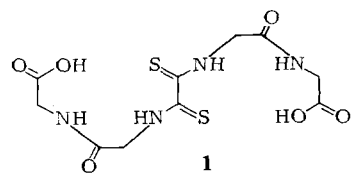
[4] The data is also consistent with rotation of the $S_3^{\ominus}$ ligand much in the same manner as π-allyl groups are known to rotate.

[5] J. E. Bercaw, *J. Am. Chem. Soc. 96* (1974) 5087.

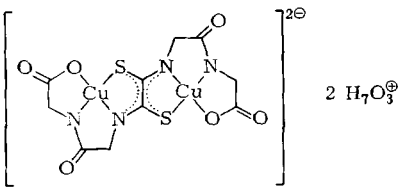
A Novel Bischelating Ligand with Two Tetradentate *N,N,O,S* Subunits—Synthesis and Properties of a Dinuclear Cu^{II} Complex

By *Jean Jacques Girerd* and *Olivier Kahn**

The synthesis of new bischelating ligands is of considerable current interest[1]. These ligands and the related dinuclear complexes have potentially a wide range of application in homogeneous catalysis, in the activation of small molecules, in electrochemistry, or as models for bioinorganic systems. Furthermore, they have provided an insight into the mechanism of the exchange interaction between metal ions[2]. In this connection, bischelating ligands able to propagate the electronic effects between metal ions far removed from each other are of particular importance. We have shown recently that an appropriate strategy to obtain such systems consisted in the design of ligands with sulfur atoms in the bridging network[3].



1



2

We report here the synthesis of the dicarboxylic acid **1** obtained from dithiooxamide $C_2S_2(NH_2)_2$ and glycylglycine $H_2NCH_2CONHCH_2COOH$ (1:2). Upon losing six protons, this molecule can function as a novel bischelating ligand with two tetradentate moieties. Indeed, the reaction of **1** and $CuSO_4 \cdot 5H_2O$ results in the dinuclear Cu^{II} complex **2**, which is insoluble in the usual protic solvents but which dissolves in basic media to give bright green solutions. The UV/VIS spectrum exhibits bands at $\lambda = 540$ ($\varepsilon = 400$) and 420 nm (1100) which are assigned to d-d and $\sigma(s)$-$d_{x^2-y^2}$ transitions, respectively.

The temperature dependence of the molar magnetic susceptibility (χ_M) between 50 and 300 K is shown in Figure 1.

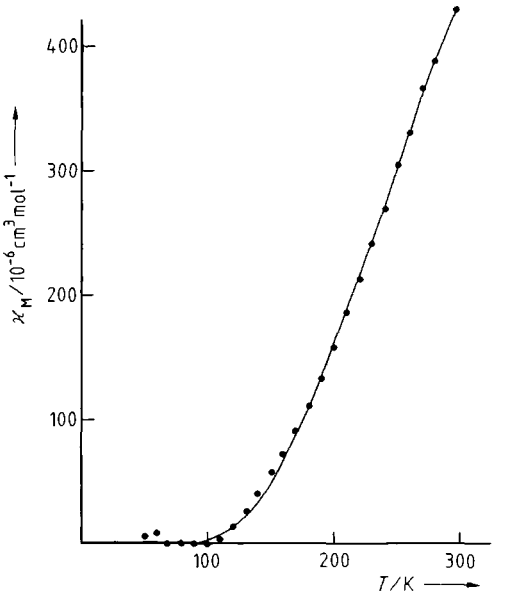


Fig. 1. Experimental and theoretical temperature dependence of the molar magnetic susceptibility (χ_M) of **2**: (•) points corrected for the non-coupled Cu^{II} impurity; (—) theoretical curve [4].

The curve is characteristic of a complex Cu^{II} dimer with very strong intramolecular antiferromagnetic coupling. The singlet-triplet energy difference J determined by a least squares fitting procedure is found to be -630 cm^{-1}[4]. This magnetic behavior is quite similar to that exhibited by the dinuclear complexes of *N,N'*-bis(2-hydroxyethyl)dithiooxamide[3]. **2** contains no COOH and NH protons, as determined by IR spectroscopy. Both the magnetic behavior and the spectroscopic properties of **2** confirm the structure of the dimeric entity shown in the formula.

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[1] See *e.g.*: U. Casellato, P. A. Vigato, D. E. Fenton, M. Vidali, *Chem. Soc. Rev. 8* (1979) 199; J. M. Lehn, *Acc. Chem. Res. 11* (1978) 49.

[2] See *e.g.*: S. L. Lambert, D. N. Hendrickson, *Inorg. Chem. 18* (1979) 2683; J. Jaud, Y. Journaux, J. Galy, O. Kahn, *Nouv. J. Chim. 4* (1980) 629.

[3] J. J. Girerd, S. Jeannin, Y. Jeannin, O. Kahn, *Inorg. Chem. 17* (1978) 3034; C. Chauvel, J. J. Girerd, Y. Jeannin, O. Kahn, G. Lavigne, *ibid. 18* (1979) 3015.

[4] The observed molar magnetic susceptibility (χ_M) was corrected for diamagnetic contributions (-370×10^{-6} cm^3 mol^{-1}) and for a small proportion of noncoupled Cu^{II} impurity, the molar magnetic susceptibility χ_M of which was assumed to follow the Curie Law $N\beta^2g^2/4kT$. The corrected susceptibility was then fitted using the expression:

$$\chi_M = \frac{2N\beta^2g^2}{kT}\left[3+\exp\left(-\frac{J}{kT}\right)\right]^{-1} + N\alpha$$

g is 2.02 and $N\alpha$ can be neglected. The "agreement factor" defined in [3] is equal to 0.8×10^{-4}.

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Crystal Structures of AlI_3, GaI_3 and InI_3—Isotypic Relationship AlI_3/SO_3**

By *Rüdiger Kniep*, Peter Blees,* and *Wolfgang Poll*

Our present state of knowledge of the crystal structures of the "simple" title compounds (and their halogen homologues) is epitomized by the citation in Wells' "Structural Inorganic Chemistry"[1]: "In contrast to crystalline $AlCl_3$ (YCl_3-type structure, Al occupies octahedral holes) $AlBr_3$ has a molecular structure (Al_2Br_6 molecules, Al occupies pairs of adjacent tetrahedral holes). The same type of molecule is found in crystalline $GaCl_3$ and InI_3 with which AlI_3 and GaI_3 are (probably) isostructural". In a communication presented at a conference, held some years earlier[2], it had been stated however that GaI_3 should have an orthorhombic octahedral layer structure, and this statement has so far never been challenged. Since no complete crystal structure analysis of AlI_3 has so far been available we have carried out crystal structure analyses on both GaI_3 and AlI_3, and at the same time have also re-determined[4] the crystal structure of InI_3[3]. The results are collected in Figure 1.

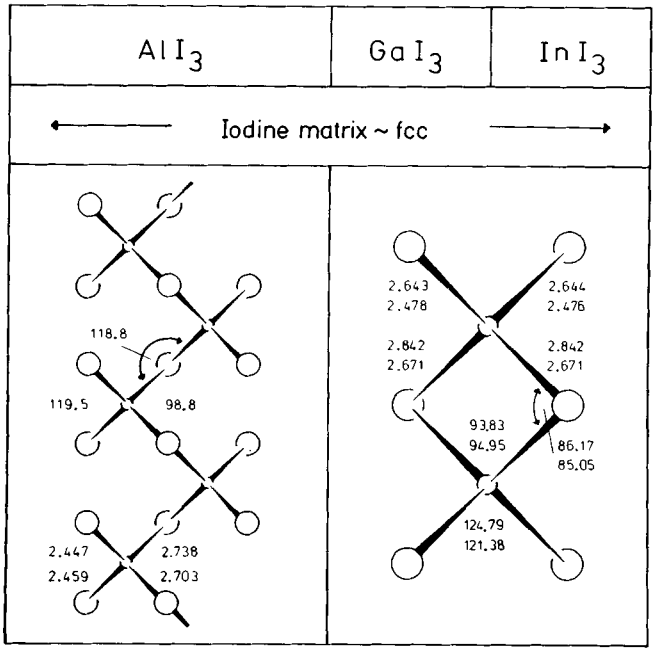

Fig. 1. Structural units in the crystal structures of AlI_3, GaI_3, and InI_3. *AlI_3*: standard deviations 0.009 Å and 0.4°, resp.; angles at Al not listed: 107.2–110.3°.—*GaI_3*: lower numerical values; standard deviations 0.002 Å and 0.07°, resp.; angles at Ga not listed: 108.90–109.76°.—InI_3: upper numerical values; standard deviations 0.002 Å and 0.06°, resp.; angle at In not listed: 107.50–109.33°.

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A feature common to all three structures is the distorted cubic close packed iodine matrix, with the metal atoms accomodated in the tetrahedral holes. GaI_3 and InI_3 are isotypic and contain dimeric molecules M_2I_6. In contrast AlI_3 has a $1/\infty$ chain structure, which is isotypic to the "asbestos-like" SO_3[5]; the concept of expected structural relationships in isoelectronic compounds[6] also proves its use here, when taking into consideration differences in electronegativity and the ratios of atomic or ionic radii.

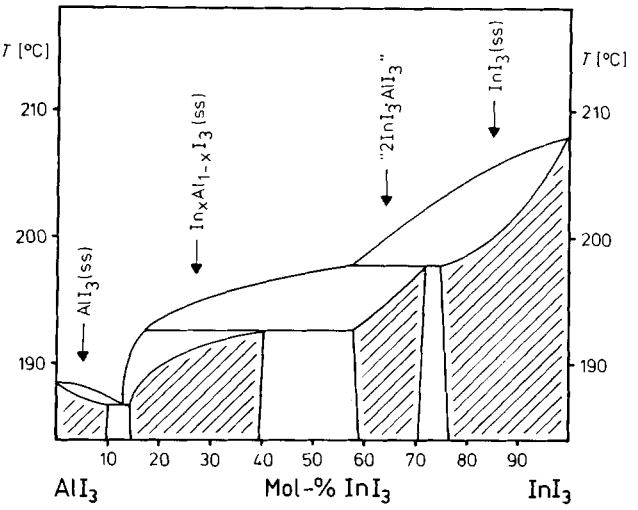

Fig. 2. Phase relationships on the quasi-binary section AlI_3-InI_3.

The structural relationships also correspond to the phase relationships on the quasi-binary sections GaI_3-InI_3 (unlimited mixed-crystal formation with minimum melting point), AlI_3-InI_3 (cf. Fig. 2), and AlI_3-GaI_3 (almost analogous to AlI_3-InI_3). With increasing InI_3 content the dimeric structure $In_xAl_{1-x}I_3$ (ss) is preferred over the chain structure AlI_3 (ss); an ordered superstructure phase "$2\,InI_3 \cdot AlI_3$" seems to occur between the isotypic substitution mixed-crystal phases $In_xAl_{1-x}I_3$ (ss) and InI_3 (ss).

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CAS Registry numbers:
AlI_3, 7784-23-8; GaI_3, 13450-91-4; InI_3, 13510-35-5

[1] A. F. Wells: *Structural Inorganic Chemistry*, 4th Ed., Clarendon Press, Oxford 1975.
[2] E. L. Amma, R. E. Rundle, *Proc. Ann. Meeting Am. Crystallogr. Assoc. 1958*, 16.
[3] J. D. Forrester, A. Zalkin, D. H. Templeton, *Inorg. Chem. 3* (1964) 63.
[4] $Mo_{K\alpha}$, Syntex $P2_1$, ω-scan, $F_0 > 3.92\sigma_F$, $2\theta_{max} = 55°$, E-XTL-program system, empirical absorption correction.
AlI_3: 1542 (641) reflections, $R = 8.4\%$; monoclinic, $P2_1/c$, $a = 9.660(2)$, $b = 6.136(1)$, $c = 11.977(3)$ Å, $\beta = 108.07(2)°$, $Z = 4\,AlI_3$.
GaI_3: 1507 (1225) reflections, $R = 9.1\%$; monoclinic, $P2_1/c$, $a = 9.607(4)$, $b = 6.079(2)$, $c = 11.856(4)$ Å, $\beta = 107.83(3)°$, $Z = 2\,Ga_2I_6$.
InI_3: 1598 (1341) reflections, $R = 8.5\%$; monoclinic, $P2_1/c$, $a = 9.852(2)$, $b = 6.110(1)$, $c = 12.206(2)$ Å, $\beta = 107.71(1)°$, $Z = 2\,In_2I_6$.
[5] R. Westrik, C. H. MacGillavry, *Acta Crystallogr. 7* (1954) 764.
[6] H. G. von Schnering, *Angew. Chem. 93* (1981) 44; *Angew. Chem. Int. Ed. Engl. 93* (1981) 33.

Ullmanns Encyklopädie der technischen Chemie (Ullmann's Encyclopedia of Industrial Chemistry). Edited by *E. Bartholomé, E. Biekert, H. Hellmann, H. Ley* (deceased), *W. M. Weigert* (deceased), and *E. Weise*. Vol. 5: *Analysen- und Messverfahren* (Analytical and Measurement Techniques). Volume editor: *H. Kelker*. Verlag Chemie, Weinheim 1980, 4th edition, xvi, 1010 pp., bound, DM 670.00.

This volume on analytical and measurement techniques which forms part of the general series of Ullmann's Encyclopedia[*] is unusual in its size: whereas the average number of pages of the previous volumes was about 700, this volume, including the German and English subject indexes, contains more than 1000 pages. Yet even at this size the editor has had difficulty in accommodating the wealth of analytical and measurement techniques relevant to the problems of industrial chemistry. The surpassing way in which he has achieved this will be seen in what follows.

Industrial measurement technology, including process analysis, *i.e.* one half of the overall topic, takes up a bare 150 pages. (Control technology was covered in Volume 4.) The present volume is thus predominantly devoted to analysis as such. Apart from the many essentially instrumental analytical methods, various general and fundamental problems and methods are dealt with. This is especially true of the introductory chapter on "Aims and methods of analysis" (25 pp.), which is also concerned with chemical analytical methods; for example in the field of organic chemistry it deals with elementary analysis and functional group analysis. It is emphasized that, despite the very high level of development of physical methods today, chemical methods are still of great importance and in many cases are irreplaceable. The other general chapters deal with digestion methods (27 pages), balances and weighing in the laboratory (8 pages), evaluation of measurements (9 pages), and the use of computers in analysis (24 pages). The instrumental techniques described are distillation (16 pages), chromatographic methods (142 pages, broken down into fundamentals, gas chromatography, thin-layer chromatography, and electrophoresis), structural analysis by crystal diffraction (34 pages), spectroscopic methods (249 pages, broken down into ultraviolet and visible, infrared and Raman spectroscopy, microwave gas spectroscopy, NMR and ESR, atomic absorption spectroscopy, emission spectroscopy, and X-ray spectral analysis), surface studies (58 pages), mass spectrometry (28 pages), electron microscopy (19 pages), polarimetry (16 pages), refractometry (10 pages), electrochemical techniques (34 pages), activation analysis (23 pages), radionuclides in analytical chemistry (8 pages), particle measuring techniques (29 pages) rheometry (23 pages), and thermal calorimetry (18 measuring techniques. All such problems can be very quickly resolved with the aid of the detailed (14 pages) subject index.

As is customary for Ullmann's Encyclopedia, the authors of the individual chapters are recognized practical experts. The overall appearance of this volume meets the quality standards to which we have grown accustomed. The editor states that his aim has been to provide a guide to the subject, and this must rank as a definite understatement. The reviewer would rather call this volume a standard work (over and above its position within the narrower framework of the encyclopedia) that will prove indispensable to any chemist who needs to make use of the techniques of instrumental analysis.

Ulfert Onken [NB 561 IE]

Spectroscopy in Heterogeneous Catalysis. By *W. N. Delgass, G. L. Haller, R. Kellerman.* and *J. H. Lunsford,* Academic Press, New York 1979, x, 341 pp., 117 figs., bound, $ 35.00.

Spectroscopic methods for the study of solid surfaces and states of chemisorption are currently in a state of such rapid development, both in numbers and in refinement, that it is often far from easy to select and use the most suitable and effective method for a given problem. This is where the present compilation should help those working in research or industry; at the same time it should act as a spur to fresh research and as an introduction to advanced students. The topics covered are infrared spectroscopy and Raman spectroscopy *(Haller),* diffuse reflection spectroscopy, including photoacoustics *(Kellerman),* Mössbauer spectroscopy *(Delgass),* electron spin resonance and nuclear magnetic resonance *(Lunsford),* and X-ray photoelectron spectroscopy *(Delgass).* With the exception of the X-PES, the methods chosen can thus be applied under the conditions of temperature and pressure usual for heterogeneous catalysis.

Each of the seven chapters comprises between 30 and 50 pages and begins with a short introduction outlining the ranges, conditions of application, and limitations of the method. There follow an introduction into the theoretical fundamentals, a presentation of the experimental layout and instrumentation, and a report on characteristic applications illustrated with examples selected from the literature. A distinction is always made between information on catalyst structures in bulk, on the surface, and on chemisorbed structures or complexes. Apart from the static state of these structures particular stress is laid upon the deter

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 (Federal Republic of Germany).

Coordination Chemistry. By *J. P. Laurent*. Pergamon Press, Oxford 1981. 200 pp., bound, £ 21.00.—ISBN 0-08-025300-8

X-Ray Diffraction by Disordered and Ordered Systems. By *D. W. L. Hukins*. Pergamon Press, Oxford 1981. ix, 164 pp., bound, £ 11.95.—ISBN 0-08-023976-5

Einführung in die chemische Thermodynamik. By *G. Kortüm* and *H. Lachmann*. 7th Edit. Verlag Chemie, Weinheim 1981. xii, 496 pp., bound, DM 98.00.—ISBN 3-527-25881-7

Nature, Aim and Methods of Microchemistry. Edited by *H. Malissa, M. Grasserbauer, R. Belcher*. Springer-Verlag, Berlin 1981. viii, 340 pp., bound, DM 88.00.—ISBN 3-211-81653-4

Physikalische Chemie der Glasoberfläche. Edited by *H. H. Dunker*. VEB Deutscher Verlag für Grundstoffindustrie, Leipzig 1981. 425 pp., bound, *ca.* DM 104.00.—Bestell-Nr. 5416288

Komplexe Prozessanalyse. Several authors. VEB Deutscher Verlag für Grundstoffindustrie, Leipzig 1982. 124 pp., brochured, *ca.* DM 19.00.—Bestell-Nr. 5416923

Gussputzen. By *Arpád Vörös*. VEB Deutscher Verlag für Grundstoffindustrie, Leipzig 1982. 203 pp., bound, *ca.* DM 44.00.—Bestell-Nr. 5416229

Houben-Weyl: Methoden der organischen Chemie. Band V/2b: Aromaten und Arine. Edited by *C. Grundmann*. Georg Thieme Verlag, Stuttgart 1981. xxxix, 797 pp., bound, *ca.* DM 680.00 (subscription price or when ordered in advance *ca.* DM 612.00).—ISBN 3-13-202704-9

Biotechnology. Vol. 1: Microbial Fundamentals. Edited by *H.-J. Rehm* and *G. Reed*. Verlag Chemie, Weinheim 1981. 520 pp., bound, DM 495.00 (subscription price DM 425.00).—ISBN 3-527-25763-2

Houben-Weyl: Methoden der organischen Chemie. Band IV/1a: Oxidation I. Compiled by *H. Blome, O. Buddenberg, P. Hartler, H. Kropf, E. Müller, A. Weickmann*, and *K. P. Zeller*. Georg Thieme Verlag, Stuttgart 1981. *Ca.* 1440 pp., bound, DM 1250.00 (subscription price or when ordered in advance DM 1125.00).—ISBN 3-13-200704-8

Organic Syntheses. Vol. 60. Edited by *O. L. Chapman*. John Wiley & Sons, Chichester 1981. xii, 140 pp., bound, £ 17.50.—ISBN 0-471-09350-9

Reactive Intermediates. Vol. 2. Edited by *M. Jones, Jr.* and *R. A. Moss*. John Wiley & Sons, Chichester 1981. 396 pp., bound, £ 38.85.—ISBN 0-471-01875-9

Max-Planck-Gesellschaft—Jahrbuch 1981. Published under the auspices of the Generalverwaltung der Max-Planck-Gesellschaft. Verlag Vandenhoeck & Ruprecht. x, 798 pp., bound, DM 70.00.—ISBN 3-525-85387-4

Shock Waves in Chemistry. Edited by *A. Lifshitz*. Marcel Dekker, Basel 1981. ix, 390 pp., bound, SFr 182.00.—ISBN 0-8247-1331-1

Datensammlung zur Toxikologie der Herbizide. 3rd instalment. Verlag Chemie, Weinheim 1981. 430 pp., loose-leaf, DM 196.00.—ISBN 3-527-25883-3

Springer Series in Chemical Physics. Vol. 18: Modelling of Chemical Reaction Systems. Edited by *K. H. Ebert, P. Deuflhard* und *W. Jäger*. Springer-Verlag, Berlin 1981. x, 389 pp., bound, DM 72.00.—ISBN 3-540-10983-8

Mössbauer Spectroscopy and Its Chemical Applications. Edited by *J. G. Stevens* and *G. K. Shenoy*. American Chemical Society, Washington 1981. 642 pp., bound, $ 69.95.—ISBN 0-8412-0593-0

Crystals—Growth, Properties, and Applications. Vol. 5: Silicon. Edited by *J. Grabmaier*. Springer-Verlag, Berlin 1981. v, 199 pp., bound, DM 110.00.—ISBN 3-540-10932-3

Polymer Science Overview: A Tribute to Herman F. Mark. Edited by *G. A. Stahl*. American Chemical Society, Washington 1981. 355 pp., bound, $ 35.95.—ISBN 0-8412-0668-6

Source Book of Food Enzymology. By *S. Schwimmer*. Avi Publishing Company, Inc., Westport, Connecticut 1981. 700 pp., bound, $ 93.50 (in den USA $ 85.00).—ISBN 0-87055-369-0

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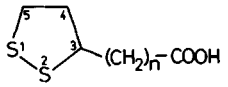
The Hydrophobic and Metal-Ion Coordinating Properties of α-Lipoic Acid— An Example of Intramolecular Equilibria in Metal-Ion Complexes

By Helmut Sigel*

Hydrophobic interactions as structure determining factors for macromolecules are well-known in biochemistry. Considerably less recognized is the fact that these low-energy interactions may also determine the structure of low-molecular species. The same applies for weak ligand-metal ion interactions. That both these factors may lead to intramolecular, concentration-independent equilibria between isomeric metal-ion complexes is demonstrated with α-lipoic acid as ligand. This cofactor offers metal ions two different binding sites: the carboxylate group and the disulfide linkage. The carboxylate group dominates the coordinating properties of this ligand towards the biologically important metal ions, but a disulfide-metal ion interaction is still possible and under sterically favorable conditions may become very important; this could also be true under enzymic conditions where the carboxyl group is no longer free but amide-linked to the protein. Furthermore, due to the valeric acid side chain, the lipoyl moiety is ideally suited to undergo hydrophobic ligand-ligand interactions in mixed-ligand complexes. Such hydrophobic interactions seem to be ideal to allow migration, *e.g.*, of the 14 Å long lipoyllysyl moiety, and also to facilitate the correct 'fixation' at the surface of the enzyme.

1. Introduction

α-Lipoic acid (1,2-dithiolane-3-valerie acid) — also known as 6,8-dithiooctanoic acid — is widely distributed in animals and plants[1]. It was discovered about 35 years ago; shortly thereafter its growth-promoting effect on certain microorganisms was recognized[2–4] and its chemical structure established[5,6] (Fig. 1)[**]. α-(+)-Lipoic acid[7] is an important protein-bound coenzyme, which *e.g.* occurs as the transacylating cofactor of several multienzymic α-keto acid dehydrogenase complexes[8–10]. Evidence that lipoic acid plays an important role in oxidative phosphorylation has also been given[11].



n = 4 : Lipoic acid (LP)
n = 2 : Bisnorlipoic acid (BL)
n = 0 : Tetranorlipoic acid (TL)

Fig. 1. Structure of α-lipoic acid and two of its analogs.

Enzyme systems that catalyze the oxidative decarboxylation of pyruvic and α-ketoglutaric acids mediated by lipoic acid have been isolated from microbial and eukaryotic cells as functional units with molecular weights in the millions[8]. For example, the pyruvate dehydrogenase multienzyme complex has been isolated from *Azotobacter, Strepto-*

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[**] Abbreviations apart from those given in Fig. 1: Ac, acetate; ATP, adenosine 5'-triphosphate; bpy, 2,2'-bipyridyl; Bnz, benzoate; Chac, 2-cyclohexylacetate; Dmds, dimethyldisulfide; Dms, dimethylsulfide; L, ligand; M, metal ion; phen, 1,10-phenanthroline; Pp, 3-phenylpropionate; Prop, propionate; Thtc, tetrahydrothiophene-2-carboxylate (thiolane-2-carboxylate); Val, valerate.

coccus, yeast, potatoes, and the hearts of mammals[1,9]. The corresponding enzyme system isolated from *Escherichia coli* and several organs of mammals has been especially well studied[8-10]. Fascinating in this connection is the question of the organization of the structure and of the reaction sequence in such a multienzyme complex. The appearance of hydrophobic interactions or the participation of labile metal ions seems possible, at least as a hypothesis.

The kinetics and regulation of pyruvate dehydrogenase kinase and pyruvate dehydrogenase phosphatase from bovine kidney and heart are partly known.[8]. Pyruvate is the substrate for pyruvate dehydrogenase and also inhibits noncompetitively the kinase which functions as regulatory subunit of pyruvate dehydrogenase. The half-maximal activity of the phosphatase is reached when the concentration of Mg^{2+} is *ca.* 2 mM; this is approximately 100 times the concentration of $Mg(ATP)^{2-}$ (*ca.* 0.02 mM) which is required to achieve half-maximal activity of the kinase[8]. Ca^{2+} is also required in addition to Mg^{2+} for pyruvate dehydrogenase phosphatase activity[12,13]. In the presence of Ca^{2+} the phosphatase binds to the transacetylase, thereby facilitating the Mg^{2+}-dependent dephosphorylation of the phosphorylated pyruvate dehydrogenase[12]. Half-maximal activity of the phosphatase is observed at a free Ca^{2+} concentration of about 1 μM. It is possible that Ca^{2+} serves as a bridge between the phosphatase and the transacetylase. Alternatively, Ca^{2+} may bind to either the phosphatase or the transacetylase, producing a conformational change that facilitates binding of the phosphatase[8]. In any case, it is clear that metal ions have some importance in these lipoic acid dependent systems.

In this connection it is also of interest that heavy-metal poisoning has been treated with lipoic acid[1,14,15], which indeed forms complexes, *e.g.* with Hg^{2+} [16,17]. The inhibition of microsomal-membrane ATPase of pigeon brain by Cu^{2+} is also reversed by lipoic acid[18]. These observations, the widespread occurrence of lipoic acid[1,7,9] and of metal ions[19] in biological systems, as well as the therapeutic use of this disulfide, stimulated investigations on the basic coordinating properties of this coenzyme.

From the structure of α-lipoic acid given in Figure 1 it is evident that this molecule has two possible binding sites for metal ions: the carboxylate group and the disulfide bridge. The coordination tendencies of these two groups in solution are now summarized and discussed in relation to their biochemical significance. Where appropriate, intramolecular hydrophobic ligand-ligand interactions in ternary complexes will also be considered.

2. Carboxylate Group: Basicity and Formation of Metal-Ion Complexes

The acidity constant of α-lipoic acid [Eq. (1)] and the stability constants of the corresponding binary complexes [Eq. (2)] have been determined by potentiometric pH-titrations (25 °C).

$$HL \rightleftharpoons H^+ + L^- \qquad K^H_{HL} = [HL]/([H][L]) \qquad (1)$$

$$M^{2+} + L^- \rightleftharpoons ML^+ \qquad K^M_{ML} = [ML]/([M][L]) \qquad (2)$$

The acidity constants obtained[20] in 50% aqueous dioxane (v/v; $I = 0.1$, $NaClO_4$) for (±)-lipoic acid ($pK^H_{HL} = 6.37$), (±)-bisnorlipoic acid (6.05), and (±)-tetranorlipoic acid (4.84) show that the acidity increases with decreasing chain length. This is in accord with the results obtained for simple carboxylic acids: valeric ($pK^H_{HL} = 6.44$)[21] < propionic (6.29)[22] < acetic (6.01)[22] ≪ formic acid (4.75)[22]. The electron withdrawal by the disulfide moiety is especially evident from a comparison of the acidity constants of acetic acid (6.01) and (±)-tetranorlipoic acid (4.84)[20]; the latter is considerably more acidic[23].

The stability of the binary 1:1 complexes of Mn^{2+}, Cu^{2+}, Zn^{2+} (cf.[20]), Cd^{2+}, or Pb^{2+} (cf.[24]) with α-lipoate is solely governed by the basicity of the carboxylate group. This is indicated by the fact that a straight line results when $\lg K^H_{HL}$ values of a series of complexes with structurally related ligands are plotted against the pK^H_{HL} values of the ligands (Fig. 2)[26,27]. It is evident that the α-lipoate complexes fit the straight "reference lines" of the binary complexes, ML^+ [Eq. (2)], of monodentate carboxylates: formate, acetate, propionate, and valerate[20-22]. As expected, there is no significant difference between the data for the (+)- and (−)-isomers of α-lipoate, or its (±)-mixture[20]. Obviously, if a metal-ion interaction with the disul-

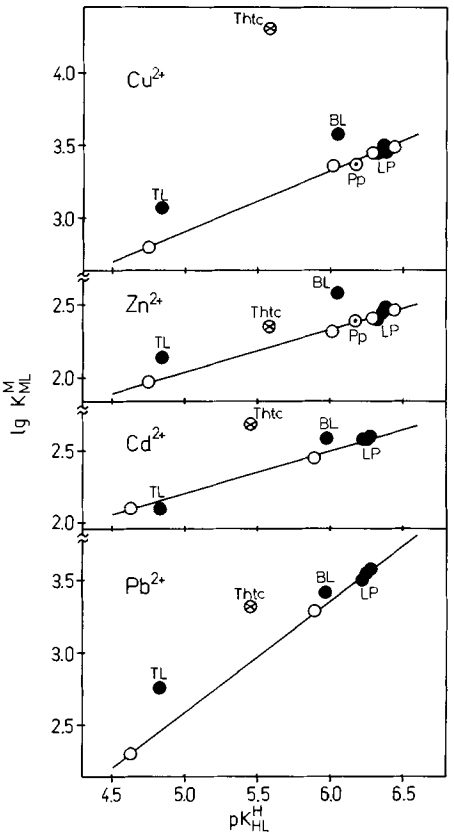


Fig. 2. Relationship between $\lg K^M_{ML}$ [Eq. (2)] and pK^H_{HL} [Eq. (1)] for the binary ML^+ complexes of α-lipoate (LP; the three points refer to (+)-, (−)-, and (±)-LP), (±)-bisnorlipoate (BL) and (±)-tetranorlipoate (TL) (●), or tetrahydrothiophene-2-carboxylate (Thtc, ⊗) and 3-phenylpropionate (Pp, ⊙; see Section 5 and Fig. 3). The reference lines are due to the corresponding complexes of the monodentate carboxylates (○) (from left to right): formate, acetate, propionate, and valerate. The plotted data ($I = 0.1$, $NaClO_4$, or $NaNO_3$; 25 °C; 50% aqueous dioxane) for the Cu^{2+} and Zn^{2+} complexes ($NaClO_4$) are taken from Table 1 of [20] and Table 2 of [25], and for the Cd^{2+} and Pb^{2+} complexes ($NaNO_3$) from Table 1 of [24].

fide moiety of α-lipoate should occur, it does not significantly increase complex stability.

However, the metal-ion complexes of the two chain-shortened lipoate analogs and of tetrahydrothiophene-2-carboxylate are clearly more stable, at least in a number of cases (Fig. 2), than expected on the basis of the basicity of the carboxylate groups alone. Here, the disulfide and the thioether groups participate in complex formation; the stability of the resulting chelates is discussed in Section 3.2.

It should be pointed out that the pK-value [Eq. (1)] of lipoic acid and the lg K-values [Eq. (2)] of the corresponding $M(LP)^+$ complexes are approximately 1.5 lg units smaller in aqueous solution. This can be estimated from the following data for acetic acid and its complexes ($I=0.1$; 25 °C). In 50% aqueous dioxane it holds that[20-22]:

$$pK^{H}_{H(Ac)} = 6.01 \pm 0.01,$$

$$\lg K^{Cu}_{Cu(Ac)} = 3.36 \pm 0.03, \quad \lg K^{Zn}_{Zn(Ac)} = 2.32 \pm 0.03$$

and in aqueous solution[28]:

$$pK^{H}_{H(Ac)} = 4.54 \pm 0.01,$$

$$\lg K^{Cu}_{Cu(Ac)} = 1.81 \pm 0.02, \quad \lg K^{Zn}_{Zn(Ac)} = 0.86 \pm 0.06.$$

The constants for (±)-lipoic acid in 50% aqueous dioxane are[20]:

$$pK^{H}_{H(LP)} = 6.37 \pm 0.01,$$

$$\lg K^{Cu}_{Cu(LP)} = 3.50 \pm 0.02, \quad \lg K^{Zn}_{Zn(LP)} = 2.47 \pm 0.02.$$

It appears safe to predict that the stability of the complexes of lipoate in water will also be solely determined by the basicity of the carboxylate group; in fact, this has already been demonstrated in the case of (+)-biotinate[29]. That the stability of complexes formed with O ligands increases as the water activity decreases is a general experience, and probably of significance for biological systems[30].

In conclusion, the dominance of the metal-ion binding properties of the carboxylate group does not mean that the disulfide moiety of lipoate does not have coordinating capacity, but only that this is not apparent under the conditions described. Moreover, it must be noted that coordination of a metal-ion to carboxylate could play a role only during the biosynthesis and metabolism[7,31-34] of lipoic acid, but not during its enzymic action since then the lipoyl moiety is amide-linked[1,8] to the enzymes and hence no longer available for coordination to a metal-ion.

3. Disulfide Coordination

3.1. Stability of Disulfide Complexes

The stability of complexes of this type with biologically important metal ions is expected to be small, but the determination of the stability constants of such weak complexes recently became possible by ^{1}H-NMR spectroscopy[35]: diamagnetic metal ions upon coordination induce a downfield shift of the resonance signals of nearby protons. The simplest ligand for such studies, which is also soluble enough in water, is dimethyl disulfide (Dmds). The stability constants of some of its complexes, according to Eq. (3), are given in Table 1.

$$M^{n+} + L \rightleftharpoons ML^{n+} \qquad K^{M}_{ML} = [ML]/([M][L]) \tag{3}$$

Table 1. Comparison of the stability of several dimethyl disulfide (Dmds) complexes with that of the corresponding dimethyl sulfide (Dms) complexes (34 °C) [a].

M^{n+}	$\lg K^{M}_{M(Dmds)}$ (D_2O)	$\lg K^{M}_{M(Dms)}$ (H_2O)	I [b]
Ca^{2+}	−1.4	−1.6	2-4.5 ($NaClO_4$)
Zn^{2+}	−1.4	−1.4	2-4.5 ($NaClO_4$)
Cd^{2+}	−1.4	−0.3 ± 0.2	2-4.5 ($NaClO_4$)
Pb^{2+}	−1.5	−1.05 ± 0.2	2-3 ($NaNO_3$)
Ag^{+}	2.01 ± 0.09	3.7 ± 0.3	0.1 ($NaNO_3$)

[a] Taken from Table 1 in [35]. Most of the given stability constants are rough estimations; unless mentioned, the lower error limit for the values is −0.5 and the upper limit +0.2 lg units. [b] The primary electrolyte is given in parenthesis.

Indeed, the stability of the complexes with the biologically important metal ions Ca^{2+} and Zn^{2+} is very low; the same is true for the heavy metal ions Cd^{2+} and Pb^{2+}.

Of course, soft[36] metal ions like Cu^+, Ag^+, or Hg^{2+} have a greater tendency to coordinate with the disulfide group, and crystal structures of disulfides, *e.g.* with Cu^+, have been determined[37,38], although coordination of these metal ions often causes cleavage of the disulfide bond[39,40]. In order to determine the stability constant of the $Ag(Dmds)^+$ complex in Table 1, the pD-value of the D_2O solution was adjusted to about 2 with DNO_3 so as to prevent cleavage of the disulfide link, a reaction which occurs at higher pH[41]. Under the conditions used, the Ag^+-Dmds solution was stable for 24 hours[35]. Attempts to study the Hg^{2+}-Dmds system failed, since a white precipitate formed[35]; this could be the nitrate salt of an $Hg(Dmds)_x^{2+}$ complex or the result of fission of the disulfide bond[42]. Furthermore, Hg_2^{2+} seemed to undergo disproportionation in the presence of dimethyl disulfide[35], in accord with earlier results[43].

All these results[35] agree well with those obtained for lipoic acid[17]: addition of lipoic acid in 95% ethanol to $Hg(NO_3)_2$ in dilute HNO_3 results in immediate formation of a heavy white precipitate which was assigned the formula $Hg(LP)(OH)_2$. From IR measurements it was concluded that the carboxylate group of lipoic acid in this compound is protonated and that Hg^{2+} coordinates to the disulfide moiety. With Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and Pb^{2+}, lipoic acid did not form isolable solids[17]; photolytic or thermal cleavage of the disulfide link was necessary before any isolable products with these cations were formed. All these metal ions, including Hg^{2+}, form insoluble solids with dihydrolipoic acid[17].

Comparison of the stability constants listed in Table 1 reveals[35] that the ligating properties of the disulfide and the thioether groups appear to be about the same for hard metal ions (*e.g.* Ca^{2+} [36]), while for several of the 'borderline' metal ions (*e.g.* Cd^{2+} [39,44] and Pb^{2+}) they are somewhat different: this means the disulfide complexes are less stable than the corresponding thioether complexes (despite the fact that the disulfide complexes with two S atoms are

statistically favored). With the soft Ag^+ these properties are even more evident: the Ag^+ complexes of dimethyl disulfide and dimethyl sulfide differ in stability by a factor of 50. This may indicate that the S_2R_2 group is somewhat less soft than the SR_2 moiety.

It may be concluded that the results shown in Table 1 are in accord with what might have been predicted[35]. Due to the $p_\pi - d_\pi$ interaction in a disulfide[1,45-47] the electrons are less available for coordination than at the thioether sulfur, hence complexes with S_2R_2 are expected to be somewhat less stable than those with SR_2.

The results described can also be viewed as a further example of the so-called α-effect, *i.e.* the observation that OH^-, for example, is a better base than OOH^-, or NH_3 than NH_2NH_2, and indeed this is also true for $S(CH_3)_2$ and $S_2(CH_3)_2$[48]. The disulfide group is less basic than the thioether sulfur, which is itself an extremely weak base ($pK_a = -6.8$)[49]. Estimations of basicity suggested the order $(CH_3)_2S > (CH_3)_2S_2 \approx CH_3SH$[48], which indicates $pK_a < -6.8$ for the disulfide moiety.

Of further interest in the present connection is a comparison of the coordinating properties of the 1,2-dithiolane moiety and those of the thiolane (tetrahydrothiophene) group. This can be carried out by comparing the stability of, for example, the Cu^{2+} complexes of tetranorlipoate and tetrahydrothiophene-2-carboxylate: as shown in Figure 2, the stabilities are respectively around 0.23 and 1.16 lg units greater than expected from the basicity of the carboxylate group (reference line). Hence, the coordination tendency of the thiolane ring is about 8-fold greater than that of the 1,2-dithiolane moiety. This indicates that this result and the corresponding observations for other metal ions (see Table 2 of Section 3.2) are in good accord with the conclusions of Table 1.

The $p_\pi - d_\pi$ interaction in disulfides is most pronounced in simple aliphatic disulfides, where the dihedral angle, *i.e.* the angle between the planes defined by RSS and SSR, is *ca.* 90° [45-47]. The SS bond length depends therefore on this angle[50,51]: for $\sphericalangle CSSC \approx 90°$ the bond length is *ca.* 202 pm, and for $\sphericalangle CSSC \approx 0°$ it is *ca.* 210 pm[52]. In the 1,2-dithiolane ring the same angle is only about 27° [1] to 35° [53], and the S—S bond length is 205.3 pm[53], *i.e.* the $p_\pi - d_\pi$ interaction is somewhat diminished[1], but the electron density available for the coordination of the metal ion at one of these sulfurs is still less than at the sulfur of the tetrahydrothiophene ring, and therefore is in agreement with the observed complex stabilities[*].

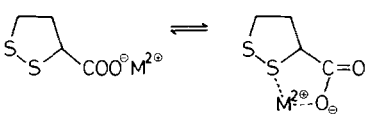
For the interaction between hard metal ions and thioethers it is known[29,44,59] that a decrease in the activity of water, *e.g.* on proceeding from water as solvent to 50% aqueous ethanol, promotes formation of the corresponding complex. The same may be surmised for the disulfide-metal ion interaction. For biological systems, this is of interest, because one may expect that at the surface of a protein the activity of water is reduced and thus a metal ion-disulfide interaction should be favored.

3.2. Formation of Chelates Involving the Disulfide Group

It is evident from Section 3.1 that the complexes formed between disulfides and those hard or 'borderline' metal ions which are important in biological systems, such as Mg^{2+}, Ca^{2+}, Mn^{2+}, Zn^{2+}, or Cu^{2+} are not very stable. However, this must not lead to the conclusion that these interactions are unimportant since, as already indicated, under conditions of reduced water activity, complex stability may increase and, more importantly, a weak interaction is enough to create specific structures, as will now be shown.

In α-lipoate the disulfide bridge and the carboxylate group are too far apart to expect a stable chelate, and this is in accord with the results of Section 2. With the chain-shortened catabolites[31,34] bisnorlipoate and tetranorlipoate (Fig. 1) the situation is different because here seven- and five-membered chelates could be formed. Indeed, the Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} complexes of (±)-tetranorlipoate and (±)-bisnorlipoate are all, with the single exception of $Cd(TL)^+$, more stable by 0.08 to 0.31 lg units than expected from the basicity of the carboxylate group of these ligands (Fig. 2). This increased stability demonstrates that the disulfide group participates in complex formation and that chelates are formed. A comparison of this increase in stability with that of the corresponding tetrahydrothiophene-2-carboxylate complexes (Fig. 2) shows that, in general, the thioether interaction is more favorable. This, however, also indicates—without any calculation being required—that the extent of chelate formation differs in these complex systems.

This implies that an intramolecular equilibrium between an 'open' and a 'closed' form exists. This is illustrated using the example of the complexes with tetranorlipoate in Eq. (4):



(4)

If the chelated isomer in which an O of the carboxylate group and an S of the disulfide moiety are coordinated is depicted as $M(L)^+_{O,S}$, and the simple carboxylate-coordi-

[*] One might be tempted to speculate that in the tetrahydrothiophene moiety the sulfur is hybridized in a more sp^3-like manner (corresponding to angles of *ca.* 109°) than S2 in the 1,2-dithiolane ring of lipoic acid. However, such a supposition would not be in agreement with the results of crystal structure determinations, where it was found that the angle around the sulfur in the tetrahydrothiophene ring (of the biotin moiety) [54] is 89.4° and the angle around the corresponding S2 in the 1,2-dithiolane ring of lipoic acid [53] is 92.8°. Hence, assuming that the angles are not different in solution, one cannot rationalize why the coordination tendency of the thioether is favored over the disulfide group. Nevertheless, it should also be added that in lipoic acid the angle at S1 is 95.5°, while at S2 it is 92.8° [53]. Hence, from the view of an orientated electron density (*i.e.* more sp^3-like) S1 should be somewhat favored [for steric reasons, only the somewhat less suitable S2 is accessible for chelate formation in tetranorlipoate (see also Section 3.2)]. In agreement with this, and possibly further favored by the steric conditions, *i.e.* the greater distance to the side chain, is the observation that S1 is the preferred reaction site in electrophilic reactions, where the steric restrictions present in chelating reactions are not imposed. For example, chemical oxidation of lipoic acid and lipoate metabolism in *Pseudomonas putida* occur preferably at S1 to form the monoxide [34]; similarly, acetylation [55] and photoreductive acylation [56, 57] at position 1 are also favored. This contrasts with a natural enzymic system [55—57] from which 6-acetyl-thio-8-mercaptooctanoic acid was isolated (see, *e.g.* also [58]); hence in enzymic systems other effects guide the reaction.

nated isomer as $M(L)_O^+$, the position of Eq. (4) may be described by the corresponding equilibrium constant K_{Ch}:

$$K_{Ch}=[M(L)_{O,S}]/[M(L)_O] \quad (5)$$

This intramolecular equilibrium constant is dimensionless and therefore independent of the absolute concentration of ML^+ [Eq. (2)]. As shown earlier[35,60], K_{Ch} may be calculated from Eq. (6),

$$K_{Ch}=\frac{K^M_{ML}}{K^M_{M(L)O}}-1 \quad (6)$$

where K^M_{ML} [Eq. (2)] is the experimentally determined constant of the isomeric complex system considered, and $K^M_{M(L)O}$ is the stability constant for the formation of the simple carboxylate-coordinated species. The crucial parameter is

$$\lg\Delta=\lg K^M_{ML}-\lg K^M_{M(L)O} \quad (7)$$

$\lg\Delta$ may be estimated from the difference between the experimentally determined value of $\lg K^M_{ML}$ for a given complex system and the corresponding "reference line" in Figure 2. Once K_{Ch} is known, the amount of $M(L)^+_{O,S}$ in Eq. (4) may also be easily obtained.

Table 2. Extent of chelate formation in binary metal-ion complexes of carboxylate ligands (L^-) with an additional sulfide or disulfide residue (in 50% aqueous dioxane; $I=0.1$; 25 °C) [a].

L^-	M^{2+}	$\lg K^M_{ML}$ [Eq. (2)]	$\lg\Delta$ [Eq. (7)]	K_{Ch} [Eq. (5)]	Amount of $M(L)^+_{O,S}$ [b] [%] [Eq. (4)]
Thtc$^-$	Mn^{2+}	1.80±0.05	≈0	≈0	≤20
	Cu^{2+}	4.31±0.03	1.16	13.5	93±1 (1)
	Zn^{2+}	2.35±0.03	0.15	0.41	29±5 (8)
	Cd^{2+}	2.68±0.02	0.34	1.2	54±2 (4)
	Pb^{2+}	3.32±0.03	0.40	1.5	60±3 (5)
(±)-TL$^-$	Mn^{2+}	1.87±0.03	≈0.04	≈0.1	≈ 9 (≤20)
	Cu^{2+}	3.07±0.03	0.23	0.70	41±4 (7)
	Zn^{2+}	2.14±0.03	0.15	0.41	29±5 (8)
	Cd^{2+}	2.10±0.04	≈0	≈0	≤11
	Pb^{2+}	2.76±0.04	0.31	1.0	50±5 (7)
(±)-BL$^-$	Mn^{2+}	2.11±0.02	≈0.16	≈0.4	≈29
	Cu^{2+}	3.58±0.02	0.23	0.70	41±3 (5)
	Zn^{2+}	2.58±0.02	0.23	0.70	41±3 (5)
	Cd^{2+}	2.58±0.02	0.09	0.23	19±4 (8)
	Pb^{2+}	3.42±0.03	0.08	0.20	17±6 (10)

[a] The entries for the first two ligands are the slightly modified results from [35]. The other results were calculated from the data published in [20] and [24]; see also Fig. 2. The error limits given for $\lg K^M_{ML}$ are *three* times the standard deviation of the mean value. [b] The error limits were calculated from the given errors for $\lg K^M_{ML}$. The values given in parenthesis were calculated by adding 0.02 log units to the errors given with $\lg K^M_{ML}$; this accounts for a possible error in the 'reference lines' which is estimated to be ≤0.02 lg units (possibly apart from the Mn^{2+} systems), because this line is based on several independent systems (Fig. 2). Hence, the values given in parenthesis can be considered as upper error limits, which might still be justified.

The results calculated for the intramolecular equilibrium constant, K_{Ch}, and the amount of 'closed' isomer $M(L)^+_{O,S}$ for the tetrahydrothiophene-2-carboxylate, (±)-tetranorlipoate, and (±)-bisnorliponate complex systems are listed in Table 2. It is evident that the percentage of the chelated isomer depends strongly on the metal ion involved: the whole range from traces to amounts close to 100% is covered. These results clearly demonstrate that the disulfide moiety does not only participate in complex formation, but *may even fix a structural arrangement* if the sulfur atom is in a sterically favorable position.

A comparison of the complexes with the sterically very similar ligands tetranorlipoate and tetrahydrothiophene-2-carboxylate shows that in the M^{2+}-Thtc$^-$ systems the amount of chelated isomer $M(L)^+_{O,S}$ is usually larger than in the M^{2+}-TL^- systems, thus confirming the somewhat better coordinating properties of thioethers compared to the disulfides (cf. Section 3.1). In addition, closer examination reveals the similar coordination tendency of Zn^{2+} towards SR_2 and S_2R_2, or the tendency of Cd^{2+} to favor SR_2. Surprisingly, the necessity of forming a seven-membered chelate does not significantly disfavor the participation of the disulfide group in bisnorlipoate complexes, compared with those of tetranorlipoate where a five-membered chelate can be formed.

Summarizing, the coordinating properties of the disulfide group favor soft metal ions, whereas their tendency to coordinate with the biochemically important hard or 'borderline' metal ions is obviously slight and apparently rather unspecific (Table 1). However, it must be emphasized that these seemingly negligible coordinating properties may lead to enhanced complex formation with ligands which have these weakly coordinating groups located close to stronger binding sites (Table 2). The most important point with regard to biological systems is that equilibration between isomers of certain complexes may be attained rather easily; a factor which could well be a key to the observed selectivity.

4. Hydrophobic Interactions in Mixed Ligand Complexes

4.1. Stability of Ternary Complexes

For the ternary complexes formed by Cu^{2+} or Zn^{2+} and 2,2′-bipyridyl (bpy) and α-lipoate or one of its chain-shortened derivatives (Fig. 1), a similar picture to that described for the binary metal ion systems (Section 2) is obtained [Eq. (8)] to a first approximation.

$$M(bpy)^{2+}+L^- \rightleftharpoons M(bpy)L^+ \quad (8)$$

$$K^{M(bpy)}_{M(bpy)L}=[M(bpy)L]/([M(bpy)][L])$$

Plots of $\lg K^{M(bpy)}_{M(bpy)L}$ against pK^H_{HL} for the ternary systems with the simple carboxylates formate, acetate, *etc.* furnish "reference lines" (Fig. 3); the values of many other systems lie relatively close to this line (usually about 0.3 lg units above it), indicating that the stability of these complexes is also determined to a large part by the basicity of the carboxylate group of the ligands.

The fact that in Figure 3 the reference line of the ternary Cu^{2+} complexes lies somewhat above the line of the binary complexes, while in the Zn^{2+} systems it lies somewhat below, is in accord with general experience[28,61-64]. In the absence of steric restrictions a *positive* value[65] for $\Delta\lg K_{Cu}$ [Eq. (9)] is obtained for the combination of a heteroaromatic N base and an O donor ligand with Cu^{2+}, *i.e.*

the mixed ligand complex [Eq. (8)] is somewhat more stable than the binary one [Eq. (2)]:

$$\Delta \lg K_M = \lg K^{M(bpy)}_{M(bpy)L} - \lg K^{M}_{ML} \quad (9)$$
$$= \lg K^{ML}_{ML(bpy)} - \lg K^{M}_{M(bpy)}$$

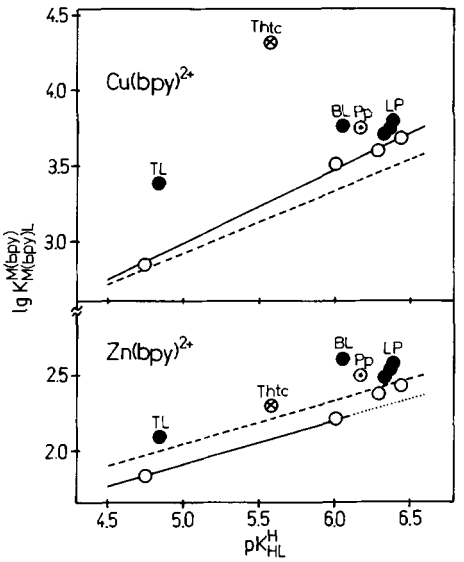


Fig. 3. Relationship between $\lg K^{M(bpy)}_{M(bpy)L}$ [Eq. (8)] and pK^{H}_{HL} [Eq. (1)] for the ternary M(bpy)L^+ complexes of α-lipoate (LP; the three points refer to (+)-, (−)- and (±)-LP), (±)-bisnorlipoate (BL) and (±)-tetranorlipoate (TL) (●), or tetrahydrothiophene-2-carboxylate (Thtc, ⊗) and 3-phenylpropionate (Pp, ⊙; see Section 5 and Fig. 2). The reference lines are due to the corresponding complexes of the monodentate carboxylates (○) (from left to right): formate, acetate, propionate, and valerate; for Zn(bpy)L^+ the reference line is only drawn through the data of formate and acetate (solid part) and then tentatively extrapolated (dotted part; cf. Section 4.2 and 4.3). The broken lines refer to the binary 1:1 complexes (Fig. 2) and are given for comparison. All the data plotted ($I = 0.1$, $NaClO_4$; 25 °C; 50% aqueous dioxane) are taken from Tables 1 and 2 of [20] and Table 2 of [25].

The same ligand combination with Zn^{2+} and other metal ions of the second half of the 3d series also leads to an enhanced stability, compared with the statistical expectation[66], but usually to a less pronounced one[28,61-64].

From the data plotted in the lower part of Figure 3 it is evident that the values for the ternary Zn(bpy)$^{2+}$ complexes with propionate and valerate, because of their enhanced stability, deviate markedly from the reference line of the corresponding complexes with formate and acetate. Similarly, for the ternary Cu(bpy)$^{2+}$ complexes of propionate and valerate a slight stability enhancement is indicated by the increased slope of the reference line (upper part of Fig. 3). The ternary complexes of both metal ions with α-lipoate and 3-phenylpropionate are *ca.* 0.2 lg units more stable than would be expected from the basicity of the carboxylate group of these ligands. Since all of these carboxylate ligands have no, or at least no easily accessible, additional binding sites, the slight but significant stability increase in the ternary lipoate and aliphatic carboxylate complexes can *only* be attributed to an intramolecular hydrophobic interaction within the mixed ligand complexes between the aromatic 2,2'-bipyridyl and the aliphatic residues of the carboxylate ligands.

For bisnorlipoate and tetranorlipoate the situation is clearly more complicated, since the disulfide groups now also become available for coordination, as is known from the corresponding binary complexes (Section 3.2). The stability and structure of the ternary complexes of these ligands will therefore be discussed separately in Section 5.

4.2. Further Evidence for Intramolecular Hydrophobic Ligand-Ligand Interactions

It is now well established that aromatic-ring stacking and hydrophobic interactions between aromatic and aliphatic groups[67] may be promoted by the formation of a metal-ion bridge between these groups, provided that suitable metal binding sites are also available[64,68-70]. Aromatic-ring stacking within mixed ligand complexes has not only been shown to occur in solution[25,64,71-75] but also in the solid state[76-79]. For the complexes considered here it is worthwhile to point out that intramolecular ligand-ligand interactions also occur in the ternary complexes of Zn(phen)$^{2+}$, or Cu(phen)$^{2+}$ and valerate[80], as indicated from the corresponding stability data.

An ideal method to establish such hydrophobic interactions more directly is ^{1}H-NMR shift measurements. Protonation or coordination of a metal ion shifts the signals of the ligand protons close to the binding site *downfield*. However, in a complex in which the aliphatic side-chain of a carboxylate is located above or below the plane of an aromatic ring, the signals of the aliphatic protons should be shifted *upfield*, relative to those of the free carboxylate, due to the ring current of the aromatic system[81]. Using NMR spectroscopy the coordination, *e.g.* of the diamagnetic Zn^{2+} (cf. also Section 3.1), and especially the ligand-ligand interaction in a ternary complex containing one ligand with an aromatic group and another with an aliphatic residue can be studied.

It is obvious that the extent of the intramolecular hydrophobic interaction in the Zn(bpy)L^+ and Zn(phen)L^+ ter-

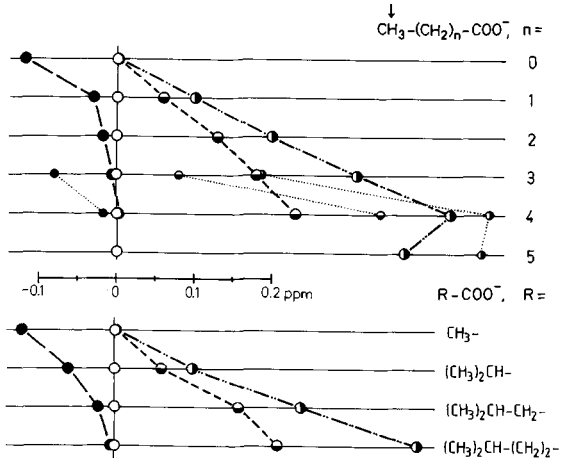


Fig. 4. Up- and down-field shifts of the terminal methyl group(s) in the ^{1}H-NMR spectra of straight-chain (upper part) and of branched-chain aliphatic carboxylates (lower part) for the Zn^{2+} (●), Zn(bpy)$^{2+}$ (◒), or Zn(phen)$^{2+}$ (◑) coordinated carboxylate ligands, relative to the resonance position of the uncoordinated carboxylates (○). For pentanoate (valerate, n = 3), hexanoate (n = 4) and heptanoate (n = 5) the resonance position of the methylene group adjacent to the terminal methyl group is also shown (smaller symbols, dotted lines). Extention of the two series was prevented by ligand insolubility. The measurements were carried out in H_2O at 35 °C. The plotted values are from [69]. Upfield shifts are positive, downfield shifts negative.

nary complexes should be dependent on the length and possibly also on the volume of the aliphatic residue of the carboxylate ligand. The results of NMR spectroscopic measurements of these complexes[69] are summarized in Figure 4: the effect which the coordination of Zn^{2+}, $Zn(bpy)^{2+}$, or $Zn(phen)^{2+}$ has on the aliphatic residue of the carboxylate ligands is quantified by plotting the *relative* position of the signal of the terminal methyl group(s) of the ligands as a function of Zn^{2+}, $Zn(bpy)^{2+}$, and $Zn(phen)^{2+}$. As expected, Zn^{2+} leads to a downfield shift and the shift difference decreases with increasing distance between the methyl group and the site of coordination. Actually, the effect is large only with acetate and falls off rapidly with increasing chain length, being already small for four-carbon chains (butyrate and 3-methylbutyrate) and negligible for longer chains. However, the upfield shift caused by $Zn(bpy)^{2+}$ and by $Zn(phen)^{2+}$ increases rapidly with increasing chain length. The larger upfield shifts due to $Zn(phen)^{2+}$ are in agreement with the larger π system of 1,10-phenanthroline and thus its larger ring current, compared to that of 2,2'-bipyridyl.

In pentanoate (valerate; n = 3 in Fig. 4), the resonance signal of the methylene group adjacent to the terminal methyl group is also shifted upfield by $Zn(bpy)^{2+}$ and $Zn(phen)^{2+}$, although less than the methyl signal itself (Fig. 4). For hexanoate (n = 4 in Fig. 4) the shifts of the methylene group adjacent to the methyl group are already larger for both ternary complexes, and for heptanoate (n = 5) $Zn(phen)^{2+}$ shifts the signal of the methylene group significantly more than the signal of the methyl group, but the signals of both groups are now shifted less than those of hexanoate. For the structure of these ternary complexes with the linear carboxylates this suggests that the "best fit" probably occurs for $Zn(phen)^{2+}$ with hexanoate and for $Zn(bpy)^{2+}$ with valerate or hexanoate[69]. A tentative structure of such a ternary complex is shown in Figure 5 for $M(bpy)(valerate)^+$ complexes.

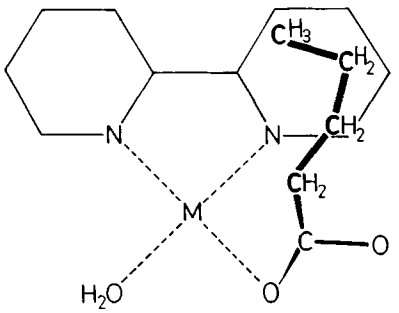


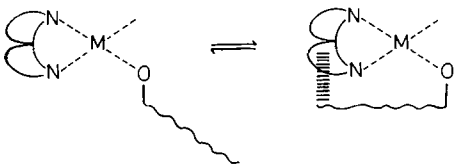
Fig. 5. Possible (schematic) structure of $M(bpy)(valerate)^+$ for the isomer with the hydrophobic ligand-ligand interaction between the alkyl residue of valerate and the aromatic ring system of 2,2'-bipyridyl.

It is interesting to note[69] that the upfield shift of the branched-chain carboxylates by $Zn(bpy)^{2+}$ and by $Zn(phen)^{2+}$ is similar to, but somewhat higher than that of the linear carboxylate of the same chain length (Fig. 4). The reason for this is probably that a somewhat higher proportion of the complex exists in the 'closed' form (see Section 4.3) due to the increased hydrophobicity of the isopropyl moiety (compared with an ethyl group).

It is possible by ^{1}H-NMR measurements to show that the aliphatic residues of such carboxylate ligands interact with 2,2'-bipyridyl and 1,10-phenanthroline also in the *absence* of metal ions. However, as expected, the adduct formation is very weak and stability constants could only be estimated[69]: $K^{(bpy)}_{(bpy)L} \simeq 1\ M^{-1}$ and $K^{(phen)}_{(phen)L} \simeq 2\ M^{-1}$ (in water). Similar results were obtained for the interaction between the isopropyl residue of L-leucine and bpy or phen[70]: $K^{(bpy)}_{(bpy)(H\cdot Leu)} = 0.6 \pm 0.4\ M^{-1}$ and $K^{(pben)}_{(phen)(H\cdot Leu)} = 1.4 \pm 0.9\ M^{-1}$ (in 25% methanol). These estimates agree well with theoretical calculations[67] for the hydrophobic interaction between leucine and phenylalanine in aqueous solution at 25 °C: $K^{(Phe)}_{(Phe)(Leu)} \simeq 2\ M^{-1}$.

4.3. Extent of the Intramolecular Ligand-Ligand Interactions

Based on the results of Section 4.2 it can readily be understood why the $M(bpy)(lipoate)^+$ complexes show enhanced stability: the valerate side chain of α-lipoate is ideally suited for hydrophobic ligand-ligand interactions. The occurrence of a complex with a structure similar to that shown in Figure 5, which is responsible for the slight increase in stability (Fig. 3) and the observed upfield shifts in the ^{1}H-NMR spectra (Fig. 4), does not imply that all the $M(bpy)(L)^+$ ternary species exist in this "folded" form. In solution there is certainly an intramolecular, and therefore concentration independent, equilibrium between an 'open' and a 'closed' form, *i.e.* between the two isomers indicated in equilibrium (10).



(10)

If these two isomers are designated as $M(bpy)(L)^{\pm}_{O}$ and $M(bpy)(L)^{\pm}_{Hy}$, the dimensionless constant of this equilibrium is defined by Eq. (11):

$$K_{Hy} = [M(bpy)(L)_{Hy}]/[M(bpy)(L)_{O}] \tag{11}$$

Values of K_{Hy} may be calculated from Eq. (12) (for details see[70]),

$$K_{Hy} = \frac{10^{\Delta \lg K_{M/exp}}}{10^{\Delta \lg K_{M/op}}} - 1 \tag{12}$$

provided values for $\Delta \lg K_{M/exp}$ and $\Delta \lg K_{M/op}$ are known [for the definition of $\Delta \lg K_M$ see Eq. (9)].

For the present cases $\Delta \lg K_{M/exp}$ for the ternary complexes of M^{2+}, bpy, and an aliphatic carboxylate or lipoate have been determined experimentally[20]. Since in $M(bpy)(HCOO)^+$ and $M(bpy)(Ac)^+$ complexes, intramolecular interaction does not occur, or is insignificant (Figs. 3 and 4)[69,80], we can use the corresponding (experimentally determined)[20] values of $\Delta \lg K_M$ for $\Delta \lg K_{M/op}$, and hence calculate K_{Hy} for the $M(bpy)(L)^+$ complexes. The K_{Hy} values in turn allow the calculation of the amount of 'closed' isomer, *i.e.* of the complex with the intramolecular hydrophobic interaction (Fig. 5). These data are assembled in

Table 3 for ternary complexes containing aliphatic carboxylates or α-lipoate.

Table 3. Estimates of the intramolecular dimensionless equilibrium constant K_{Hy} [Eqs. (11) and (12)] and of the amount of "closed" isomer [Eq. (10)] for the ternary complexes M(A)(B), with an intramolecular ligand-ligand interaction between a heteroaromatic N ligand (A) and a second ligand (B) with an aliphatic moiety (50% aqueous dioxane; $I = 0.1$, $NaClO_4$; 25 °C) [a].

No. M(A)(B) [a]		$\Delta\lg K_{M/exp}$	$\Delta\lg K_{M/op}$	$\Delta\Delta\lg K_M$ [Eq. (11, 12)] [b]	K_{Hy}	Amount of $M(A)(B)_{Hy}$ [Eq. (10)] [%]
1	Cu(bpy)(HCOO)$^+$	0.04	0.10	—	—	—
2	Cu(bpy)(Ac)$^+$	0.15				
3	Cu(bpy)(Prop)$^+$	0.15	0.10	≈0.05	≈0.12	≈11
4	Cu(bpy)(Val)$^+$	0.19	0.10	0.09	0.23	19
5	Cu(bpy)((+)-LP)$^+$	0.34	0.10	0.24	0.74	43
6	Cu(bpy)((−)-LP)$^+$	0.25	0.10	0.15	0.41	29
7	Cu(bpy)((±)-LP)$^+$	0.24	0.10	0.14	0.38	28
8	Zn(bpy)(HCOO)$^+$	−0.14	−0.12	—	—	—
9	Zn(bpy)(Ac)$^+$	−0.11				
10	Zn(bpy)(Prop)$^+$	−0.03	−0.12	0.09	0.23	19
11	Zn(bpy)(Val)$^+$	−0.04	−0.12	0.08	0.20	17
12	Zn(bpy)((+)-LP)$^+$	0.11	−0.12	0.23	0.70	41
13	Zn(bpy)((−)-LP)$^+$	0.08	−0.12	0.20	0.58	37
14	Zn(bpy)((±)-LP)$^+$	0.07	−0.12	0.19	0.55	35
15	Cu(phen)(HCOO)$^+$	0.06	0.05	—	—	—
16	Cu(phen)(Ac)$^+$	0.04				
17	Cu(phen)(Prop)$^+$	0.10	0.05	0.05	0.12	11
18	Cu(phen)(Val)$^+$	0.17	0.05	0.12	0.32	24
19	Cu(phen)(Chac)$^+$	0.26	0.05	0.21	0.62	38
20	Zn(phen)(HCOO)$^+$	−0.14	−0.15	—	—	—
21	Zn(phen)(Ac)$^+$	−0.16				
22	Zn(phen)(Prop)$^+$	−0.11	−0.15	0.04	0.10	9
23	Zn(phen)(Val)$^+$	−0.02	−0.15	0.13	0.35	26
24	Zn(phen)(Chac)$^+$	0.06	−0.15	0.21	0.62	38

[a] The constants for $\Delta\lg K_{M/exp}$ were taken for No. 1–14 from [20] and for No. 15–24 from [80]. Part of the results concerning the simple carboxylates are also given in Table 3 of [29]. [b] $\Delta\Delta\lg K_M = \Delta\lg K_{M/exp} - \Delta\lg K_{M/op}$ (see text); *i.e.*, this value is the decisive parameter of Eq. (12).

It must be emphasized that the values of K_{Hy} and the resulting amounts given in Table 3 can only be considered as estimates, because they are derived from differences between stability constants which are connected with a certain experimental error. On the other hand, it should also be pointed out that by using the difference $\Delta\Delta\lg K_M$ (see footnote [b] in Table 3) in these calculations, systematic errors cancel to a large part[70]. Indeed, the trends indicated by the results are highly reasonable, *i.e.* the amount of 'closed' isomer increases with increasing chain length of the aliphatic carboxylate: propionate < valerate < α-lipoate. Similarly, an increase in the size of the aromatic ring system also favors hydrophobic interaction, provided the chain of the aliphatic carboxylate is long enough, *e.g.* for valerate $M(bpy)^{2+}$ (No. 4,11) < $M(phen)^{2+}$ (No. 18,23) holds. That an increase in the size of the alkyl group of the aliphatic carboxylate also favors the 'closed' isomer is to be expected: clearly, the hydrophobic interaction of $M(phen)^{2+}$ with 2-cyclohexylacetate (No. 19,24) is more pronounced than with valerate (No. 18,23).

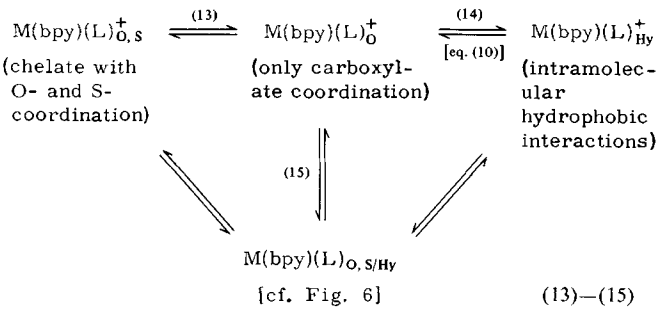
No significance should at present be attached to the seemingly different extents of intramolecular hydrophobic interactions in the ternary complexes containing the optical isomers of α-lipoate; here, very careful investigations of the indicated trends would be necessary before any conclusions should be drawn. But it may be added that the amounts given in Table 3 for the $M(bpy)(lipoate)^+_{Hy}$ complexes are very similar to those calculated recently[29] for the corresponding complexes with (+)-biotin: 29 and 31% for $M(bpy)((+)\text{-biotinate})^+_{Hy}$ with $M^{2+} = Cu^{2+}$ or Zn^{2+}, respectively. This result is gratifying because both the ligands lipoate and biotinate contain a valerate side chain.

That the properties of the Cu^{2+} and Zn^{2+} complexes may differ somewhat is to be expected because Cu^{2+} prefers a square-planar (or grossly distorted octahedral) coordination sphere, while that of Zn^{2+} is octahedral (or tetrahedral). These different geometries could, in certain cases[70], lead to a somewhat different intramolecular ligand-ligand interaction, though it appears for the systems in Table 3 that this is not very significant.

It is instructive to compare the results of Table 3 from an energetic point of view with the theoretical calculations of *Scheraga*[67], who calculated that at 25 °C $\Delta G° = -1.7$ kJ/mol for the hydrophobic interaction between the phenyl residue of phenylalanine and the isopropyl moiety of leucine in aqueous solution. By considering the whole range of the $\Delta\Delta\lg K_M$ values (0.04–0.24 log units) listed in Table 3 a value of $\Delta G° = -0.23$ to -1.4 kJ/mol is calculated. This means that the agreement between the theoretical and experimental data is highly reasonable, especially if it is considered that in the present examples the aliphatic group is often not branched, and that the theoretical calculation of *Scheraga* is based on a maximal interaction; it is obvious that in the ternary complexes the mobility of the ligands is restricted and, therefore, that the interaction is often not sterically ideal.

5. Are There Isomeric Equilibria Involving the Coordination of Disulfide *and* a Hydrophobic Interaction?

In binary complexes of the chain-shortened catabolites of α-lipoate, namely bisnor- und tetranorlipoate (Fig. 1), the disulfide group participates in complex formation by forming seven- and five-membered chelates, respectively (Section 3.2). However, these ligands also have aliphatic moieties of five and three carbon atoms; from the results outlined in Sections 4.2 and 4.3 it is clear that this is sufficient for a hydrophobic interaction with the aromatic system of 2,2′-bipyridyl in ternary $M(bpy)L^+$ complexes. Hence, at least from a theoretical point of view, the following intramolecular equilibria become possible[*]:



[*] Assuming that equilibria (13) and (14) operate, Eq. (8) may be rewritten as Eq. (16):

$$M(bpy)^{2+} + L^- \rightleftharpoons [M(bpy)(L)^+_{O,S} + M(bpy)(L)^+_{Hy} + M(bpy)(L)^+_O]$$

$$K^{M(bpy)}_{M(bpy)L} = ([M(bpy)(L)_{O,S}] + [M(bpy)(L)_{Hy}] + [M(bpy)(L)_O])/([M(bpy)][L] \quad (16)$$

Bearing this scheme in mind we may now consider the increased stabilities (see Fig. 3) of the ternary complexes $M(bpy)L^+$, where L is bisnorlipoate, tetranorlipoate, tetrahydrothiophene-2-carboxylate, or 3-phenylpropionate. In ternary complexes of the last mentioned ligand only aromatic-ring stacking is possible because, apart from the carboxylate group, this ligand offers no metal-ion binding site[**]. A comparison of the increase in stability of $M(bpy)(Pp)^+$ with that of $M(bpy)(BL)^+$ reveals for both Cu^{2+} and Zn^{2+} that the ternary bisnorlipoate complexes are more stable (Fig. 3). Since intramolecular hydrophobic interactions are somewhat less pronounced than aromatic-ring stacking interactions, *i.e.* they contribute less to the overall stability[70], it follows that in the ternary $M(bpy)(BL)^+$ complexes a metal ion-disulfide interaction must also exist, which is responsible for this additional increase in stability.

Another relatively clear-cut case is that of $Cu(bpy)(Thtc)^+$, where due to the square-planar coordination sphere of the metal ion a chelated tetrahydrothiophene-2-carboxylate cannot simultaneously undergo a ligand-ligand interaction with the 2,2′-bipyridyl, which is also coordinated. Furthermore, a Cu^{2+}-thioether interaction is expected[62] to be of about the same extent in binary and ternary complexes, *i.e.* $\Delta\lg K_{Cu} \simeq 0$. Indeed, *e.g.* for $Cu(bpy)(CH_3CH_2—S—CH_2COO)^+$, $\Delta\lg K_{Cu} = -0.01$[82] and for $Cu(bpy)(Thtc)^+$, $\Delta\lg K_{Cu} = 0.01$[21]. Hence, the whole increase in stability observed for this ternary complex in (Fig. 3) may be attributed solely to a Cu^{2+}-thioether interaction: the complex is present in 92% as the chelated isomer $Cu(bpy)(Thtc)^+_{O,S}$ (Table 4); in fact, this percentage is, within the error limits, identical to the 93% calculated for the binary $Cu(Thtc)^+_{O,S}$ species (Table 2).

Reconsidering $Cu(bpy)(BL)^+$ ($\Delta\lg K_{Cu} = +0.18$[20]), for which it was already concluded that in addition to the metal ion-disulfide coordination a hydrophobic ligand-ligand interaction must also occur, it may be assumed—based on the results with $Cu(bpy)(Thtc)^+$—that the Cu^{2+}-disulfide interaction is also about the same in $Cu(BL)^+$ and $Cu(bpy)(BL)^+$. The values given in Table 4 for $Cu(bpy)(BL)^+_{O,S}$, $Cu(bpy)(BL)^+_{Hy}$, and $Cu(bpy)(BL)^+_O$ were tentatively estimated using this assumption. The corresponding arguments may be advanced for the $Cu(bpy)(TL)^+$ system ($\Delta\lg K_{Cu} = +0.31$[20]) by taking into account the results for $Cu(bpy)(benzoate)^+$; again it can be concluded that both types of interactions exist, *i.e.* that equilibria (13) and (14) are important. The tentatively estimated amounts of the isomers are also given in Table 4.

There is one further aspect to be mentioned for $Cu(bpy)(BL)^+$ and $Cu(bpy)(TL)^+$. Assuming that an apical Cu^{2+}-disulfide coordination occurs, a simultaneous hydrophobic interaction becomes possible (*vide infra;* Fig. 6). Apical (axial) coordination of the disulfide bridge of this type has recently been shown to occur in crystals of the Cu^{2+} complex of oxidized glutathione[83]: the long Cu—S distance of 3.22 Å indicates that this interaction is weak and probably non-existent in aqueous solution. However, occurrence of the isomers $Cu(bpy)(BL)^+_{O,S/Hy}$ and $Cu(bpy)(TL)^+_{O,S/Hy}$ in trace amounts cannot be excluded at present.

[**] Eq. (19) therefore simplifies to $K_{I(tot)} = K_{Hy}$.

Table 4. Intramolecular isomeric equilibria in the ternary complexes, $M(bpy)(L)^+$, which involve *S*-coordination and/or interactions (50% aqueous dioxane; $I = 0.1$, $NaClO_4$; 25 °C)[a, b].

$M(bpy)(L)^+$	$\lg K^{M(bpy)}_{M(bpy)L}$ [Eq. (8, 18)]	$\lg\Delta$ [c]	$K_{I(tot)}$ [Eq. (19, 20)]	Amount of $M(bpy)(L)^+_{I(tot)}$ [%]	$M(bpy)(L)^+_{O,S}$ [Eq. (13)] [%] [b]	$M(bpy)(L)^+_{Hy}$ [Eq. (10, 14)] [%] [b]	$M(bpy)(L)^+_{O,S/Hy}$ [Eq. (15)] [%] [b]	$M(bpy)(L)^+_O$ [%]
$Cu(bpy)(Thtc)^+$	4.32 ± 0.03	1.07	11	92 ± 1 (1)	92			8
$Cu(bpy)((\pm)\text{-}TL)^+$	3.38 ± 0.04	0.44	1.8	64 ± 3 (5)	*41*	*23*		36
$Cu(bpy)(Bnz)^+$	3.58 ± 0.03	0.18	0.51	34 ± 5 (8)	—	34	—	66
$Cu(bpy)((\pm)\text{-}BL)^+$	3.76 ± 0.02	0.32	1.1	52 ± 2 (4)	*41*	*11*		48
$Cu(bpy)(Pp)^+$	3.75 ± 0.02	0.26	0.82	45 ± 3 (5)	—	45	—	55
$Zn(bpy)(Thtc)^+$	2.30 ± 0.03	0.23	0.70	41 ± 4 (7)			*41*	59
$Zn(bpy)((\pm)\text{-}TL)^+$	2.09 ± 0.03	0.23	0.70	41 ± 4 (7)			*41*	59
$Zn(bpy)(Bnz)^+$	2.40 ± 0.03	0.17	0.48	32 ± 5 (8)	—	32	—	68
$Zn(bpy)((\pm)\text{-}BL)^+$	2.61 ± 0.04	0.40	1.5	60 ± 4 (6)			*60*	40
$Zn(bpy)(Pp)^+$	2.50 ± 0.01	0.25	0.78	44 ± 1 (4)	—	44	—	56

[a] These results were calculated from the data published in [20–22, 25]; see also Fig. 3. The error limits given for $\lg K^{M(bpy)}_{M(bpy)L}$ are *three* times the standard deviation of the mean value; see also footnote [b] of Table 2. [b] The percentages printed in *italics* are assigned tentatively. [c] This is the crucial parameter of Eq. (20). For the ternary Cu^{2+} complexes the difference between the experimental value and the reference line of the *binary* complexes (see Fig. 3; upper part) was taken and 0.10 lg units (= average of $\Delta\lg K_{Cu}$ of $Cu(bpy)(HCOO)^+$ and $Cu(bpy)(Ac)^+$; cf. Table 3) were deducted to account for the formation of the ternary complexes. For the ternary Zn^{2+} complexes, $\lg\Delta$ corresponds to the difference between the experimental value and the reference line (Fig. 3; lower part).

With Eq. (16), $K^{M(bpy)}_{M(bpy)(L)O}$ (*i.e.* the formation constant of the simple carboxylate coordinated species), K_{Hy} [Eq. (11)], and $K_{O,S}$ [Eq. (17); cf. Eq. (13)] equation (18) may be derived [35, 60, 70]:

$$K_{O,S} = [M(bpy)(L)_{O,S}]/[M(bpy)(L)_O] \quad (17)$$

$$K^{M(bpy)}_{M(bpy)L} = K^{M(bpy)}_{M(bpy)(L)O}(1 + K_{O,S} + K_{Hy}) \quad (18)$$

The difficulty will certainly be to determine, independently of one another, the intramolecular constants $K_{O,S}$ and K_{Hy}, while it should be easier to determine their sum, *i.e.* the constant due to the *total* intramolecular interaction:

$$K_{I(tot)} = K_{O,S} + K_{Hy} \quad (19)$$

Obviously, $K_{I(tot)}$ is also the equilibrium constant for Eq. (15) if the *total* disulfide and hydrophobic interaction occurs within the same ternary species, *i.e.* if Eq. (13) and (14) do not exist. Should equilibria (13), (14) *and* (15) exist simultaneously, then the situation is even more complicated.

From Eq. (18) and (19), Eq. (20) can be derived:

$$K_{I(tot)} = \frac{K^{M(bpy)}_{M(bpy)L}}{K^{M(bpy)}_{M(bpy)(L)O}} - 1 \quad (20)$$

Eq. (20) may now be used analogously to Eq. (6) for calculations.

It has already been concluded that both types of interactions must be present in the ternary complex $Zn(bpy)(BL)^+$ and the corresponding arguments also hold for $Zn(bpy)(TL)^+$ and $Zn(bpy)(Thtc)^+$; the observed increased stabilities (Fig. 3; Table 4) cannot be *solely* attributed to hydrophobic interaction *or* to disulfide coordination (cf. Table 2). However, with the octahedral (or tetrahedral) coordination sphere of Zn^{2+} a disulfide coordination (approximately normal to the ring)[29,46,84] and a hydrophobic ligand-ligand interaction are simultaneously possible (as may also be seen from molecular models); this situation is depicted in Figure 6. Since this structure, which allows both kinds of interactions, seems energetically favored relative to $Zn(bpy)(L)^+_{O,S}$ and $Zn(bpy)(L)^+_{Hy}$, it was assumed in Table 4 that these isomers occur only in trace amounts, whereas $M(bpy)(L)^+_{O,S/Hy}$ is the predominant isomer.

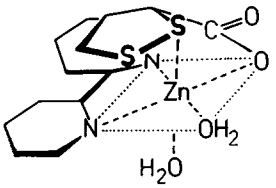


Fig. 6. Possible (schematic) structure of the isomer with a Zn^{2+}-disulfide coordination and a hydrophobic ligand-ligand interaction of the ternary complex-system formed by Zn^{2+}, 2,2'-bipyridyl, and tetranorlipoate.

In conclusion it is clear that the mixed ligand complexes containing bisnorlipoate or tetranorlipoate exist in isomeric equilibria and that both metal ion-disulfide and hydrophobic ligand-ligand interactions are important. However, it is also clear that at present the amounts of the several isomers may only be assigned tentatively.

6. Conclusions Concerning the Properties of the Lipoyl Residue

If lipoic acid is linked to an amino group in a protein as an amide[1,8], the 1,2-dithiolane moiety will remain rather flexible. So far, it is not known whether a metal ion-disulfide interaction occurs during the biochemical reactions in which the lipoyl group is involved, but the results (Section 3) show that this possibility should be considered. A weak disulfide-metal ion interaction of this type could create the active enzyme-substrate complex. Furthermore, taking into account that the electron density at the two sulfur atoms is apparently not equivalent (Section 3.1)[52], this would allow coordination of a metal ion (if sterically possible) at S1, thereby creating an electron deficiency at S2. This could stimulate hydride transfer from an appropriate substrate. The result would be rupture of the S-S bond and formation of the reduced species, dihydrolipoic acid. Obviously, instead of a hydride any other suitable group could be transferred to such a metal ion-activated species.

It should also be added that, in agreement with general observations[85], reduction of the disulfide bond of the lipoyl moiety results in two RS^- groups, which are much stronger binding sites for most metal ions[17]. This is probably the reason why lipoic acid could be used[1,14,15,17] in the treatment of heavy-metal poisoning.

The sterically correct 'fixation' of the lipoyl moiety at the surface of the protein might be further promoted, or even solely achieved (*i.e.* without a metal ion-sulfur coordination), by hydrophobic interactions. From Section 4 (and 5) it is evident that an intramolecular ligand-ligand interaction of this type occurs in mixed-ligand metal-ion complexes containing an aromatic moiety and the lipoyl group. In enzymic systems a corresponding interaction, *e.g.* between a tryptophanyl residue and the valeric acid side chain of the lipoyl moiety, also appears to be possible. Moreover, the need for a sterically correct 'fixation' of the lipoyl moiety seems apparent: In the pyruvate and α-ketoglutarate dehydrogenase complexes of *Escherichia coli*[8] the carboxyl group of lipoic acid is amide-linked to the ε-amino group of a lysyl residue of the protein, providing a flexible arm of about 14 Å for the reactive dithiolane ring; the lysyl residue also has hydrophobic properties[29]. A schematic representation of the possible rotation of such a lipoyllysyl moiety within a multienzyme complex is shown in Figure 7.

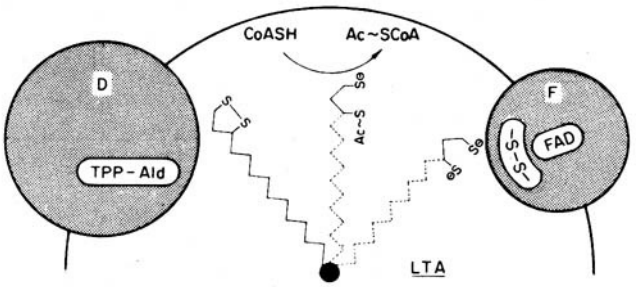


Fig. 7. Schematic representation (after *Reed* [8]) of the possible rotation of a lipoyllysyl chain between α-hydroxyethylthiamine pyrophosphate (TPP-Ald) bound to pyruvate dehydrogenase (D), the site for acetyl transfer to CoA (coenzyme A), and the reactive disulfide of the flavoprotein (F). The lipoyllysyl moiety is an integral part of dihydrolipoyl transacetylase (LTA). Reproduced by permission of the author and the American Chemical Society.

It appears that the dynamic features which are involved in the lipoyl-enzymic process require distinct structural conditions (Fig. 7). But it also seems clear that these structural conditions should readily be brought about to allow the 'cyclic' transformations of the dithiolane ring. The disulfide-metal ion coordination and the hydrophobic interactions described appear to meet this condition from an energetic point of view. The values of $\lg\Delta$ (Tables 2 and 4) and $\Delta\Delta\lg K_M$ (Table 3) range from 0.04 to 0.44 lg units, corresponding to $\Delta G^0 = -0.23$ to -2.5 kJ/mol. In summing up it becomes clear that the lipoyl moiety is very versati'e in its ability to interact with other molecules or ions.

7. Outlook

What have we learned, aside from the special case of 'lipoic acid'? In other words, can the results described be generalized?

Certainly, metal ions are abundant and clearly play an important role in biology[19], and *Wood*, in a slight overstatement, formulated[86]: "If you think that biochemistry is the organic chemistry of living systems, then you are

misled; *biochemistry is the coordination chemistry of living systems*". Indeed, it appears that an interaction between metal ions and disulfide or thioether groups is inevitably to be expected, since these groups are also rather abundant, occurring, *e.g.* in cystine[39], lipoic acid, the oxidized form of glutathione[40], methionine[39,87], *S*-methylcysteine[39,87], penicillin[87], and (+)-biotin[29]. The most well-known example is presumably the coordination of Cu^{2+} to the thioether group of a methionyl residue in plastocyanin, a 'blue' copper protein[88].

It is evident from the results summarized in this article that an interaction is also to be expected between such S donors and other biologically important, but compared to Cu^{2+} less coordinating[30,89] metal ions like Zn^{2+} or Mn^{2+}, possibly even Mg^{2+} and Ca^{2+}. The crucial point is that the *stability of a complex* may well be determined, *e.g.* by the coordination to a carboxylate group, but that the *structure of the complex* is governed by a sterically favorably positioned thioether or disulfide group. This additional interaction then causes *intra*molecular equilibriation between isomers, the position of these equilibria being independent of the concentration! Assuming that an isomer of this type has a structure which makes it the 'reactive' substrate for a particular reaction, a 'flowing' or a 'cyclic' process may be relatively easily sustained, because the energy needed for the interconversion of the isomers is small. For an alteration of the position of such an equilibrium, a change in the water structure is already enough, as it occurs *e.g.* at the surface of a protein. It will not be simple to detect such weak interactions between metal ions and thioether or disulfide groups, but a specific search now appears possible and rewarding.

This also holds for the structuring action of the hydrophobic interactions between aliphatic or aromatic groups, including aliphatic-aromatic interactions[67]. For these interactions, *e.g.* the purine bases of nucleotides[72-76,90], the indole residue of tryptophan[72,75], or the isopropyl moiety of leucine are especially suitable[70]. Indeed, it has already been established that the corresponding ligand-ligand interactions occur in ternary complexes and the positions of the intramolecular equilibria have been estimated[64,70,91]. That such hydrophobic interactions can lead to stereoselectivity has been demonstrated recently with Cr^{3+} and Co^{3+} complexes[92].

The interplay between high- and low-molecular weight ligands *via* the interactions described is evident from the following example. Carbonic anhydrase is a zinc-metalloenzyme whose active site is in a protein cavity having hydrophobic properties[93,94]. This enzyme is inhibited by the monoanions of sulfonamides[93,95,96], those with an aromatic residue being especially effective, and this indicates the occurrence of hydrophobic interactions[96]. It is also remarkable that the apoenzyme binds sulfonamides, *e.g.* acetazolamide (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide) but the affinity is approximately a factor of 1000 less than that of the native Zn^{2+}-enzyme[95]; indeed monoanions[93,94], including those of sulfonamides[97], also coordinate to the metal ion[96]. The cooperative effect observed here may be explained by observations obtained with low-molecular ternary complexes: *firstly*, the combination of donor atoms bound to a metal ion is important, whereby imidazole groups, in particular, may increase stability[61-63][*]; such groups are coordinated to Zn^{2+} in carbonic anhydrase[62,93]. *Secondly*, the hydrophobic interactions[70,91] as described here, also enhance the stability of the complex. Both points are certainly responsible for many of the cooperative effects observed in biological systems.

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[*] The combination of heteroaromatic N-bases with O-donors (or groups with O-donor-like properties, *e.g.* nitrogen in R—C(O)NH$^-$ [62]) results in increased stability of the ternary complexes with Mn^{2+}, (Fe^{2+}), Co^{2+}, Ni^{2+}, Cu^{2+}, or Zn^{2+} [61—65].

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Which Factors Determine the Reactivity and Regioselectivity of Free Radical Substitution and Addition Reactions?

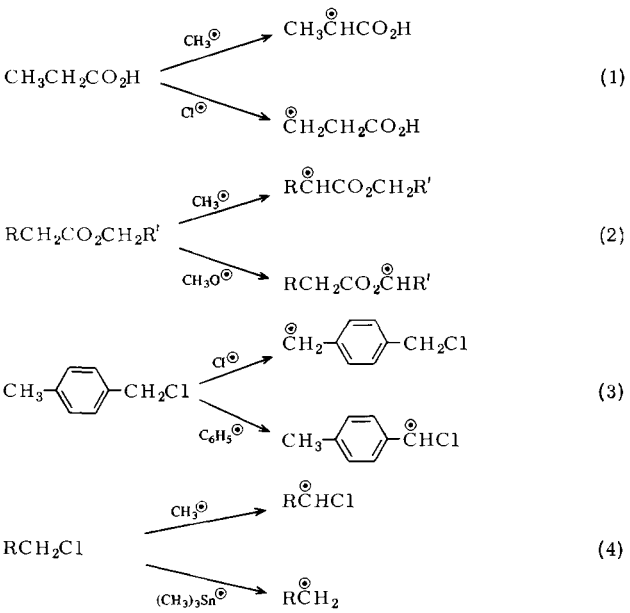
By John M. Tedder*

The relative importance of bond strength, steric effects, and polarity in determining the rate and orientation of free radical substitution and free radical addition reactions is considered. The factors which control substitution reactions (radical transfer reactions) are gathered together as five "rules", and a similar five "rules" are proposed for addition reactions. These "rules" are shown to be special cases of two "laws" which govern all free radical reactions.

1. Introduction

At first sight we might expect it would be easier to unravel the directive effects which control free radical reactions than it would be to elucidate the factors which control ionic reactions in solution. In the long run this will probably prove to be so. However, when we first look at free radical reactions we find them, in many ways, to be more complicated than heterolytic processes in solution. For example, in electrophilic aromatic substitution a substituent (*e.g.* methyl) will be *ortho-, para*-directing and activating—no matter what electrophile (*e.g.* $NO_2^{\oplus}$ or $CH_3CO^{\odot}$ or SO_3) is involved.

There are however many examples of radical substitution (*i.e.* transfer) reactions where different radicals attack different sites:



(1)

(2)

(3)

(4)

Scheme 1.

Scheme 1 contains examples of four different regioselectivities exhibited in radical transfer reactions; the regioselectivity is dependent on the attacking radical.

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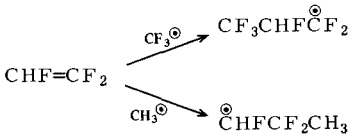
Examples (1) to (3) are reactions in which the different radicals (or atoms) abstract hydrogen atoms from the same substrate, whereas in example (4) the different radicals abstract different atoms (methyl radicals abstract hydrogen while trimethyltin radicals abstract chlorine).

Similarly, the orientation of electrophilic addition to unsymmetric olefins is the same regardless of the electrophile, but in free radical addition different radicals add preferentially to different sites of the substrate.



(5)

Scheme 2.

Scheme 2 shows the predominant orientation of addition of methyl and trifluoromethyl radicals to trifluoroethylene

2. Factors which Control the Regiospecificity and Relative Rate of Free Radical Transfer Reactions[3]

We will first discuss radical reactions which lead to substitution, more particularly reactions in whose product-determining step, a hydrogen atom is transferred from substrate to the radical.

$$R{-}H + X^{\odot} \rightarrow R^{\odot} + H{-}X$$

Table 1 shows the logarithm of the pre-exponential factors (A) and the activation energies for the abstraction of H

Table 1. Arrhenius parameters for H-abstraction from methane by various atoms and radicals $R^{\odot}$ [1]. D(R—H) = bond dissociation energy [2].

$CH_4 + R^{\odot} \rightarrow CH_3^{\odot} + R{-}H$

$R^{\odot}$	log$A$ [L mol^{-1} s^{-1}]	E_A [kcal mol^{-1}]	D(R—H) [kcal mol^{-1}]
$F^{\odot}$	11.1	1.2	136
$Cl^{\odot}$	10.4	3.9	103
$Br^{\odot}$	11.0	18.6	87
$CH_3^{\odot}$	8.8	14.3	104
$CF_3^{\odot}$	9.2	11.5	106
$CH_3O^{\odot}$	8.8	11.0	104

from methane. The pre-exponential terms for the radicals are approximately two orders of magnitude less than for the atoms because of the loss of rotational entropy in forming the transition state. Table 1 also shows there is no simple relationship between the strength of the bond being formed (D(R—H)) and the activation energy (E_A).

The first factor we will consider is the strength of the bond being broken.

2.1. Strength of the Bond Broken and the Evans-Polanyi Relationship

Table 2 shows that A varies very little with the site of attack (marked with asterisk). The changes in rate constant k are entirely due to differences in the activation energy term. Plotting the determined activation energies against the strength of the C—H bond being broken leads to a straight line. Such relationships are called Evans-Polanyi equations:

$$E_A = \alpha[D(\text{R—H})] + \beta$$

Table 2. Arrhenius parameters for H-abstraction from alkanes by methyl radicals at 164 °C [1c].

Alkane	log$A$ [L mol^{-1} s^{-1}]	E_A [kcal mol^{-1}]	log$k$ [L mol^{-1} s^{-1}]
$\overset{*}{C}H_4$	8.76	14.23	1.65
$CH_3\overset{*}{C}H_3$	8.83	11.83	2.96
$CH_3\overset{*}{C}H_2CH_3$	8.82	10.13	3.75
$(CH_3)_3\overset{*}{C}H$	8.38	8.03	4.36

Similar straight line plots have been observed for the reaction of other radicals with the alkanes listed in Table 2 (see Table 3).

Table 3. Evans-Polanyi parameters for the reaction of radicals and atoms with alkanes (RH) [2].

$$RH + X^{\odot} \rightarrow R^{\odot} + HX$$

$X^{\odot}$	α	β [kcal mol^{-1}]
$CH_3^{\odot}$	0.49	74
$CF_3^{\odot}$	0.53	84
$Br^{\odot}$	0.86	83
$I^{\odot}$	0.91	69

The existence of Evans-Polanyi relations emphasizes the importance of the strength of the bond being broken. However, no linear relationship of this kind is to be expected when the polarity changes from reaction to reaction. The constant α would be expected to increase as the reaction became more endothermic (*i.e.* more selective), and Table 3 shows that α increases with the endothermicity of the reactions from methyl radicals, to bromine atoms, to iodine atoms. The constant α for trifluoromethyl radicals, however, is greater than that for methyl radicals even though the trifluoromethyl radical reactions are exothermic. The difference is that trifluoromethyl radicals are "electrophilic" and hydrogen abstraction is facilitated at the more electropositive centers (*i.e.* *tert* > *sec* > *prim* > CH_4). This is one of the many examples we will find in which the most reactive radical is also the most selective[4].

Later we will discuss the effect of polarity on the transition state, but in any discussion of bond strength it is important to remember that an unsymmetric bond is usually stronger than a similar symmetric bond (*i.e.* $D(\text{ABX—XAB}) < D(\text{A}_2\text{X—XB}_2)$); this is due to the presence of some ionic character in the unsymmetric bond. It is necessary to distinguish this ground state effect on bond dissociation energy from the polar effect in the transition state of a radical transfer reaction.

2.2. Steric Effects and Their Influence on Radical Transfer Reactions

There are three types of steric effects which are likely to be important in radical transfer reactions: steric hindrance, which inhibits the primary radical approaching a particular reaction site; steric inhibition of resonance, which prevents the incipient radical from being stabilized by electron delocalization; and finally steric compression, which is partly released in forming the new radical. All three types of steric effect are important in free radical reactions, but some release of steric compression must occur in every abstraction reaction. The familiar decrease in C—H bond strengths from primary to secondary to tertiary, can be attributed partly to steric compression which is released when the incipient radical forms[5,6]. The relative strength of C—H bonds has also been attributed to stabilization of the incipient radical by hyperconjugation, but, as we shall see, there is good evidence that resonance stabilization is only of minor importance.

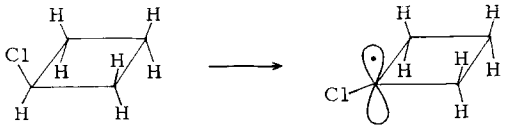
Table 4 lists the Arrhenius parameters for H-abstraction from cyclopentane, cyclohexane, and cycloheptane. It is seen that the activation energy for H-abstraction from cyclohexane is always greater than for that from either cyclopentane or cycloheptane. This difference in E_A between cyclopentane and cycloheptane, on the one hand, and cyclohexane on the other is attributed to the presence of torsional strain in the former two compounds, which is released when the corresponding radical (or cation) is formed. In contrast, cyclohexane is free from torsional strain.

Table 4. Arrhenius parameters for H-abstraction from cyclopentane, cyclohexane, and cycloheptane by $Br^{\odot}$ and other radicals (A in L mol^{-1} s^{-1}, E_A in kcal mol^{-1}) [7].

	$Br^{\odot}$		$CF_3^{\odot}$		$C_2F_5^{\odot}$		$CH_3^{\odot}$		$CCl_3^{\odot}$	
	log$A$	E_A	log$A$	E_A	log$A$	E_A	log$A$	E_A	log$A$	E_A
Cyclopentane	11.6	9.4	9.3	6.2	8.6	5.7	8.9	9.5	9.0	10.7
Cyclohexane	12.2	11.5	9.1	6.3	8.6	5.8	9.1	9.9	8.8	10.7
Cycloheptane	11.4	8.0	9.4	6.0	9.0	5.7	9.9	9.3	9.1	9.9

Another example of the release of steric compression comes from the chlorination of chlorocyclobutane[8]. The rate of H-abstraction from the α-position of this compound by chlorine atoms is five times faster than abstraction from the α-position of chlorocyclohexane, notwithstanding the effect of Walsh orbitals (which lead to a strengthening of the cyclobutane exocyclic bonds). Again,

the formation of the (1-chlorocyclobutyl) radical is accompanied by the release of steric strain.

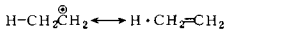
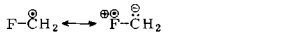
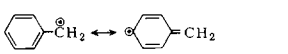
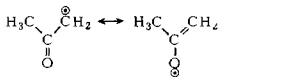
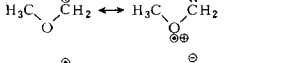
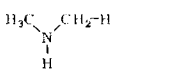
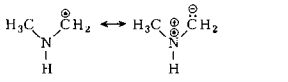


2.3. Electron Delocalization and its Influence on Bond Strength

Electron delocalization plays a large part in any theoretical account of heterolytic reactions. It is natural, therefore, that the concept should be applied to homolytic processes. Table 5 lists the Arrhenius parameters for H-abstraction from substituted methanes (R—CH_3), where substituent R provides varying possibilities of delocalizing an unpaired electron.

Table 5. Arrhenius parameters for H-abstraction from substituted methanes by methyl radicals at 164 °C [1c].

$RCH_3 + \overset{\odot}{C}H_3 \rightarrow R\overset{\odot}{C}H_2 + CH_4$

RCH_2—H	Resonance	log$A$ [L mol^{-1} s^{-1}]	E_A [kcal mol^{-1}]	k [L mol^{-1} s^{-1}]
CH_3CH_2-H		8.1	10.4	8.0×10^2
FCH_2-H		8.2	11.8	2.0×10^2
$CH_3CH{=}CHCH_2$-H		8.1	7.6	2.0×10^4
$C_6H_5CH_2$-H		8.6	9.5	7.1×10^3
CH_3COCH_2-H		8.5	9.7	4.5×10^3
CH_3OCH_2-H		8.6	10.0	4.0×10^3
		8.4	8.9	8.9×10^3

The surprising feature of the data in Table 5 is not the evidence for "resonance stabilization", but how small the effect turns out to be. There is a wider variation of reactivity in H-abstraction from the series CH_3—H to $(CH_3)_3C$—H (see Table 2) than for those compounds in Table 5. In other words, although electron delocalization of the unpaired electron in the incipient radical affects the strength of the bond undergoing fission, the effect is much smaller than might be expected from our knowledge of heterolytic processes.

"Resonance stabilization" of the unpaired electron requires that the half-filled orbital of the radical center possesses a symmetry such that it can overlap with an adjacent p-AO or π-MO. Overlap of this type may be restricted by steric factors.

A related phenomenon is the stereoelectronic effect, *i.e.* the steric requirements for the delocalization of non-bonding electrons[9]. For example, hydrogen abstraction by *tert*-butoxyl radicals from the two dioxanes **A** and **B** proceeds more than ten times faster from **A**, than from **B**. The important difference is that the axial hydrogen atom in **A** is antiperiplanar to the shaded sp^2 orbitals on the oxygen atoms allowing orbital interaction. No such interaction is possible with **B**.

2.4. Strength of the New Bond being Formed

If the strength of the bond broken is important, it follows that the strength of the bond being formed will also be important. Table 6 shows the relative selectivities for H-abstraction from simple alkanes by the four halogen atoms. The transition from the very exothermic fluorine atom reaction to the almost equally endothermic iodine atom reaction is associated with a change in rate constant (at 150 °C) of nearly fifteen orders of magnitude. As shown in Section 2.5, the polarity of the transition state plays an important role in determining selectivity. In the present case, however, the halogen atoms are all electronegative species and hence polarity only makes a small contribution to the very dramatic changes in selectivity observed in Table 6.

Table 6. Relative selectivities for H-abstraction from ethane, propane, and isobutane by halogen atoms in the gas phase [1].

Atom	T [°C]	CH_3—	$CH_2<$	$CH\leqslant$	D(X—H) [kcal mol^{-1}]
$F^\odot$	25	1	1	2	136
$Cl^\odot$	25	1	4	7	103
$Br^\odot$	150	1	80	2000	87
$I^\odot$	150	1	1000	97000	71

It is often asserted that free radical reactions are unselective, particularly when compared to reactions like aromatic nitration. Table 6 shows that free radical substitution can be extremely selective; for example, bromination of *iso*-butane leads almost exclusively to 2-bromo-2-methylpropane.

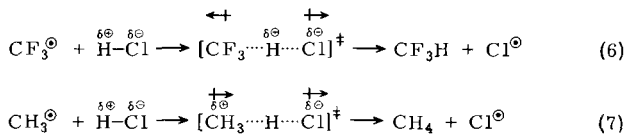
2.5. Importance of Polarity in Radical Transfer Reactions

Table 7 shows the activation energies for a series of radical transfer reactions in which the heat of reaction (ΔH) is very small, *i.e.* the reactions are nearly thermoneutral. The very striking feature of these data is the low energy barrier

Table 7. Activation energies for nearly thermoneutral radical transfer reactions involving small molecules (Forward reaction: (1); reverse reaction: (2); E_A in kcal mol^{-1}) [1, 2].

Reaction	E_A (1)	E_A (2)	ΔH_1
$CH_3^\odot + CH_4 \rightleftharpoons CH_4 + CH_3^\odot$	14.0	14.0	0
$CF_3^\odot + CH_4 \rightleftharpoons CF_3H + CH_3^\odot$	11.2	11.5	−0.3
$CH_3^\odot + HCl \rightleftharpoons CH_4 + Cl^\odot$	2.5	3.5	−1.0
$CF_3^\odot + HCl \rightleftharpoons CF_3H + Cl^\odot$	5.0	8.0	−3.0

for the reactions involving hydrogen chloride. The lowering of the energy barrier is due to polar forces in the transition state. It is very significant that while the activation energy for H-abstraction from methane by trifluoromethyl radicals is lower than that for abstraction by methyl radicals, the order is reversed in the H-abstractions from hydrogen chloride. This is because in the latter reactions the "electronegative" ("electron attracting") trifluoromethyl radical resists formation of a polar transition state, while the "electropositive" ("electron supplying") methyl radical facilitates the formation of a polar transition state:

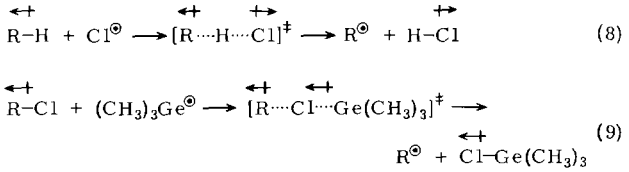


Scheme 3.

Evidence for the importance of polar forces in determining the course of radical transfer reactions is well documented. Relationships of the Hammett $\sigma\rho$-type have been thoroughly investigated for H-transfer reactions involving halogen atoms[10]. Perhaps one of the most convincing arguments for the importance of polarity in radical reactions is that groups which facilitate hydrogen abstraction by one radical retard H-abstraction by another.

2.6. Reversal of the Polarity Effect

If we consider a molecule R—H, in which R contains electronegative substituents close to the hydrogen atom to be abstracted by a chlorine atom, the R—H bond will be polarized and the formation of the hydrogen chloride will be opposed.



Scheme 4.

If we now consider a similar molecule R—Cl in which R again contains an electronegative substituent close to the chlorine atom, which this time is to be abstracted by trimethylgermyl radicals, the polarization of the R—Cl bond will now assist the formation of trimethylgermyl chloride (Scheme 4, examples (8) and (9)). This "reversal" of the polarity effect is illustrated in Table 8.

Other examples of the "reverse" polarity effect have been reported, especially Hammett relationships with positive ρ values[12].

Table 8. Relative rate constants of Cl-abstraction from R—CCl_3 molecules by trimethylgermyl radicals in the gas phase at 25 °C [11].

$(CH_3)_3Ge^{\odot} + R—CCl_3 \rightarrow (CH_3)_3GeCl + RCCl_2^{\odot}$

R	CH_3	CH_2Cl	$CHCl_2$	CF_3
k_{rel}	1	3.1	7.5	9.2

2.7. Combination of Steric, Resonance, and Polar Effects

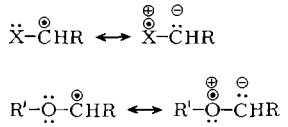
The relative reactivity of different sites in an alkane towards attack by a radical, *i.e.* tertiary, secondary, or primary, is best interpreted in terms of release of steric compression.

Resonance stabilization *via* hyperconjugation is of minor importance. An electron-repelling inductive effect will augment the effect of steric compression when the attacking atom or radical is "electrophilic". Thus, attack on branched chain alkanes by bromine will be enhanced by the inductive effect of adjacent alkyl substituents, whereas the more or less "nucleophilic" methyl radicals will be retarded. Table 9 shows that the polar effect is larger than we might have expected. The H-abstractions by methyl radicals are slightly exothermic, whereas the abstractions by bromine atoms are endothermic (even for *iso*-butane). We would therefore expect bromine to be the more selective although, because of the higher pre-exponential factors (A) associated with atom reactions, the differences in rate constants might not be large. In fact, as Table 9 shows, the rate of H-abstraction from molecular hydrogen by bromine atoms is two orders of magnitude less than abstraction by methyl radicals. In sharp contrast, bromine atoms abstract hydrogen from *iso*-butane two orders of magnitude faster than methyl radicals. Once again we have polarity overriding bond strengths.

Table 9. Arrhenius parameters for H-abstraction from simple alkanes by methyl radicals and bromine atoms ($\log A$ in L mol^{-1} s^{-1}; E_A in kcal mol^{-1}) [1].

R	$CH_3^{\odot}$		$Br^{\odot}$		$\frac{\log k(Br^{\odot})}{\log k(CH_3^{\odot})}$
	$\log A$	E_A	$\log A$	E_A	
H—H	8.6	10.5	10.7	17.5	−2.4
CH_3—H	8.8	14.2	10.6	18.6	−0.5
CH_3CH_2—H	8.8	11.8	10.9	13.4	+1.3
$(CH_3)_2CH$—H	8.8	10.1	10.7	10.1	+1.9
$(CH_3)_3C$—H	8.3	8.0	10.3	7.5	+2.5

As reagents, *i.e.* as attacking atoms, the halogens are "electrophilic" species, but as substituents, in addition to being "electronegative", they can also behave as electron donors.



Exactly the same is true for the alkoxy group, both as a radical (*e.g.* $CH_3O^{\odot}$) and as a substituent. There is comparatively little data about ethers or alkoxyl radicals, but there are considerable good kinetic data about chlorine and fluorine as substituents.

Table 10 shows that although we can rationalize the experimental data, prediction of the relative reactivities using qualitative arguments is very difficult. Very electronegative substituents have the effect of strengthening adjacent C—H bonds, and in the case of fluorine this is in opposition to any delocalization of the unpaired electron which may be possible. The introduction of one fluorine atom substituent into methane (*e.g.* CH_3F) lowers the activation

Table 10. Arrhenius parameters for H-abstraction from methane and its chloro- and fluoro-derivatives by $CH_3^{\odot}$, $CF_3^{\odot}$, and $Br^{\odot}$ ($\log A$ in L mol^{-1} s^{-1}; E_A in kcal mol^{-1}) [1].

Substrate	$CH_3^{\odot}$		$CF_3^{\odot}$		$Br^{\odot}$	
	$\log A$	E_A	$\log A$	E_A	$\log A$	E_A
CH_3—H	8.8	14.2	9.2	11.5	11.0	18.6
FCH_2—H	8.2	11.8	9.1	11.2	10.7	16.1
F_2CH—H	8.0	10.4	8.9	11.2	10.4	15.6
F_3C—H	7.4	13.6	—	—	10.1	22.3
$ClCH_2$—H	—	— [a]	9.1	10.6	10.9	14.7
Cl_2CH—H	—	— [a]	9.1	10.6	10.0	10.9
Cl_3C—H	—	— [a]	8.1	6.6	9.4	9.3

[a] No reliable data available.

energy for H-abstraction, the effect being greatest for methyl radicals where polarity enhances reactivity. A second fluorine atom substituent (CH_2F_2) further enhances H-abstraction by methyl radicals, but retards abstraction by trifluoromethyl radicals to a small extent (clearly a polar effect). The third fluorine atom substituent, as in fluoroform, greatly strengthens the C—H bond. It is noticeable however that in bromination the bond strength effect is supplemented by a deactivating polar effect, whereas in attack by methyl radicals the polar effect is activating (*i.e.* in bromination, CF_3H is less reactive than CH_4, whereas in attack by methyl radicals the reverse is true). The reactivity of chloroform is in sharp contrast to fluoroform. It is by far the most reactive of the chloromethanes and this is undoubtedly attributable to release of steric strain as the trichloromethyl radical is formed.

3. Summary of Section 2; Five Rules for Radical Transfer Reactions

Free radical substitution is a two stage process involving two discrete atom (or group) transfers. In the examples discussed, the overall reaction is determined by the initial atom transfer. In terms of simple rate theory the reaction is governed by two terms, the pre-exponential factor (A) and the activation energy (E_A). The A-factor varies by nearly three orders of magnitude depending on whether the primary species is an atom or a radical. However, A-factors vary very little from radical to radical or to changes in the substrate molecule. We can thus reduce the variables which control free radical substitution reactions, to two, apart from the almost constant pre-exponential factor. These are the relative strengths of the bonds being broken and formed, and polarity in the transition state. The way in which these two interrelated factors operate can best be summarized in *"Five Rules of Radical Substitution"*.

Rule 1

If there is little polarity in the transition state (or if polarity is constant in the reaction series) the relative rates of atom transfer by a particular radical will depend on the strengths of the bonds being broken (the Evans-Polanyi relationships). The strength of the bond being broken can be regarded as being affected (apart from polarity) by: a) resonance stabilization of the incipient radical, and b) the extent to which steric compression is released in forming the new radical.

Rule 2

The strength of the bond formed will largely control the selectivity of the reaction. If there is no polarity in the transition state the selectivity of a particular radical will depend on the heat of reaction (ΔH large and positive indicates a very selective reaction, ΔH large and negative means a very unselective reaction).

Rule 3

In thermoneutral reactions the rate of atom transfer is very dependent on the degree of polarity in the transition state.

Example: nonpolar transition state

$$H^{\odot} + CH_4 \rightarrow H_2 + CH_3^{\odot}$$
$\Delta H \simeq -1$ kcal mol^{-1}; $E_A = 11.9$ kcal mol^{-1}

Example: polar transition state

$$CH_3^{\odot} + HCl \rightarrow CH_4 + Cl^{\odot}$$
$\Delta H \simeq -1$ kcal mol^{-1}; $E_A = 2.5$ kcal mol^{-1}

Rule 4

Radicals (or atoms) which lead to polar transition states can be regarded as "electronegative" (e.g. the halogens) or "electropositive" (e.g. trimethylgermyl radicals). Electron withdrawing substituents will enhance transfer reactions by electropositive radicals and retard reactions with electronegative radicals. In reactions where ΔH is small this can mean that the more reactive radical is also the more selective

Example: reversal of substituent effects (X = H or F)

$$X—CCl_2—H + Br^{\odot} \xrightarrow{k_x} X—CCl_2^{\odot} + HBr$$
$k_H/k_F = 25$

$$X—CCl_2—Cl + (CH_3)_3Ge^{\odot} \xrightarrow{k_x} X—CCl_2^{\odot} + (CH_3)_3GeCl$$
$k_H/k_F = 0.1$

Rule 5

In exothermic reactions the transition state is "early" and although polarity may be important, neither release of steric strain nor delocalization of the unpaired electron in the incipient radical are important. In contrast in endothermic reactions, polarity will still be significant but both release of steric strain and delocalization of the unpaired electron are important

Example: exothermic reactions (early transition state, influence of polarity neutralizes the bond strength)

$$Cl^{\odot} + CHCl_3 \xrightarrow{a} HCl + CCl_3^{\odot}$$

$$Cl^{\odot} + CH_4 \xrightarrow{b} HCl + CH_3^{\odot}$$

$k_a/k_b = 1.0$ (164 °C)

Example: endothermic reactions (late transition state, steric release overrides polarity)

$$Br^{\odot} + CHCl_3 \xrightarrow{a} HBr + CCl_3^{\odot}$$

$$Br^{\odot} + CH_4 \xrightarrow{b} HBr + CH_3^{\odot}$$

$k_a/k_b = 1000$ (164 °C)

$D(CCl_3—H) = 95.7$ kcal·mol^{-1}; $D(CH_3—H) = 104$ kcal·mol^{-1}

4. Factors which Control the Regiospecificity and Relative Rate of Free Radical Addition Reactions[3, 7]

The activation energies for radical addition to ethylene are usually substantially lower than those for H-abstraction from methane. As in radical transfer reactions the pre-exponential term (A) is two to three orders of magnitude larger for reactions of atoms than for reactions of radicals, because of the loss of rotational entropy when the radicals start to form a new bond.

Table 11. Arrhenius parameters for the addition of $H^{\odot}$, $CF_3^{\odot}$ and $CH_3^{\odot}$ to ethylene at 164 °C [1b].

	log$A$ [L mol^{-1} s^{-1}]	E_A [kcal mol^{-1}]	k [L mol^{-1} s^{-1}]
$H^{\odot}$	11.0	2.8	3.9×10^9
$CF_3^{\odot}$	8.0	2.9	3.5×10^6
$CH_3^{\odot}$	8.5	7.7	4.5×10^4

4.1. Strength of the Bond Being Formed and Steric Compression

In radical transfer reactions we saw that release of steric compression played an important role in determining the strength of the bond being broken, and hence the ease of H-abstraction. In radical addition, exactly the reverse process occurs and we would therefore expect the relative magnitude of the steric compression to be important.

The big difference between ionic and radical addition reactions is illustrated in Table 12. Cationic addition occurs preferentially at the CH_2-end of propene and at the CF_3CH-end of 3,3,3-trifluoropropene, *i.e.* at opposite ends of the double bond. No such reversal is observed in free radical addition, and indeed there is as yet no well-established report of preferential addition to the substituted end of a monosubstituted olefin (*i.e.* for the olefins in Table 12, addition is always preferentially at the α-position). This includes an enormous range of substituents and is clearly associated with steric compression in the adduct radical.

We commented on the relative strengths of symmetric and similar unsymmetric bonds in our discussion on radical transfer reactions in Section 2.1. The same applies to CC double bonds; thus, the π-bond in 1,1-difluoroethene is stronger than that in either ethene or tetrafluoroethene. The activation energies and relative rates of addition reflect this (cf. relative rates at 164 °C:

$$CF_3^{\odot} + CH_2{=}CH_2 \qquad k_{rel} = 1$$

$$CF_3^{\odot} + CH_2{=}CF_2 \qquad k_{rel} = 0.15$$

$$CF_3^{\odot} + CF_2{=}CF_2 \qquad k_{rel} = 0.12$$

$$CF_3^{\odot} + CH_2{=}CF_2 \qquad k_{rel} = 0.006$$

Table 12. Relative rates and regioselectivity in the addition of $CH_3^{\odot}$ und $CF_3^{\odot}$ to some substituted ethylenes 164 °C [3]; k_c = rate constant for addition to ethylene.

Olefin $\overset{\alpha}{CH_2}{=}\overset{\beta}{CH}—X$	Regioselectivity (α : β)		k_α/k_c	
	$CH_3^{\odot}$	$CF_3^{\odot}$	$CH_3^{\odot}$	$CF_3^{\odot}$
$CH_2{=}CH—CH_3$	1 : 0.2	1 : 0.1	0.7	2.3
$CH_2{=}CH—CF_3$	1 : 0.3	1 : 0.02	0.9	0.4
$CH_2{=}CH—F$	1 : 0.2	1 : 0.09	0.9	0.5
$CH_2{=}CH—CH{=}CH_2$	1 : 0.01	1 : > 0.01	8.1	20

4.2. Electron Delocalization in the Adduct Radical

Electron delocalization plays an important role in any treatment of directive effects in ionic reactions. This is usually attributed to resonance stabilization (*i.e.* to lowering of the electronic energy of the adduct ion), but it seems likely that in solution dispersion of the charge associated with the resonance is more important than the electronic energy. Table 12 shows that radicals attack the unsubstituted end of vinyl fluoride preferentially, because attack at the substituted end is retarded (*i.e.* steric compression) and not because attack at the unsubstituted end is enhanced. Table 13 lists the Arrhenius parameters for trifluoromethyl radical addition to a wide variety of monosubstituted olefins, and also indicates possible delocalization of the electron in the adduct radical. In practice the

Table 13. Possible resonance stabilization of adduct radicals at 164 °C [7]; k_c = rate constant for addition to ethylene.

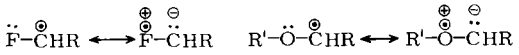
$CF_3^{\odot} + CH_2{=}CHX \rightarrow CF_3CH_2C^{\odot}HX$

X	Resonance structures	k/k_c	log$A$ [L mol^{-1} s^{-1}]	E_A [kcal mol^{-1}]
H	$CF_3CH_2\overset{\oplus}{C}H_2$	1	8.0	2.9
F	$CF_3CH_2\overset{\oplus}{C}H{-}F \leftrightarrow CF_3CH_2\overset{\ominus}{C}{-}\overset{\oplus}{F}$	0.5	7.9	3.3
Cl	$CF_3CH_2\overset{\oplus}{C}H{-}Cl \leftrightarrow CF_3CH_2\overset{\ominus}{C}{-}\overset{\oplus}{Cl}$	1.3	7.8	2.3
Br	$CF_3CH_2\overset{\oplus}{C}H{-}Br \leftrightarrow CF_3CH_2\overset{\ominus}{C}{-}\overset{\oplus}{Br}$	1.2	7.8	2.2
—CN	$CF_3CH_2\overset{\oplus}{C}H{-}C{\equiv}N \leftrightarrow CF_3CH_2CH{=}C{=}\overset{\oplus}{N}$	0.7	7.4	2.1
$\overset{O}{\overset{\|}{C}}{-}CH_3$	$CF_3CH_2\overset{\oplus}{C}H{-}C(CH_3){=}O \leftrightarrow CF_3CH_2CH{=}C(CH_3){-}\overset{\oplus}{O}$	2.1	7.9	1.8

rates of addition are almost identical to each other, and the exclusive addition of $CF_3^{\odot}$ to the unsubstituted end of some of the olefins is entirely due to deactivation (attributable to steric compression) at the substituted end.

As shown in Table 12, the addition to butadiene is appreciably faster than addition to any of the other olefins and this is clearly attributable to electron delocalization.

We conclude that electron delocalization involving CC π-orbitals can play an important part in determining the rate and regiospecificity of radical addition reactions. On the other hand, unsymmetrical π-orbitals in the nitrile group or the carbonyl group are less willing to donate electrons from the more electronegative nitrogen or oxygen atoms and therefore have little activating effect. Electron delocalization involving non-bonding electrons also only plays a minor role, probably because such delocalization involves separation of charge, *e.g.*



4.3. Steric Requirements of the Attacking Radical

If our picture of increasing steric compression as the attacking radical forms a bond with one end of an olefin is correct, the actual "bulk" of the radical will affect the regiospecificity of the reaction. Table 14 shows that rate constants for addition of alkyl radicals to ethylene decrease as the bulk of the radical increases.

Table 14. Relative rate constants for the addition of alkyl radicals to ethylene at 164 °C [7].

Radical	$CH_3^{\odot}$	$CH_3CH_2^{\odot}$	$(CH_3)_2CH^{\odot}$	$(CH_3)_3C^{\odot}$
k_{rel}	1.0	0.8	0.5	0.2

The effect of the bulk of the attacking radical on the regiospecificity is shown in Table 15.

Table 15. Regiospecificity and rate of the addition of fluoroalkyl radicals to vinyl fluoride at 164 °C [7]; k_c = rate constant for addition to ethylene.

Radical	$\overset{\alpha}{C}H_2=\overset{\beta}{C}HF$	
	α : β	$2k_\alpha/k_c$
$CF_3^{\odot}$	1 : 0.1	0.5
$CF_3CF_2^{\odot}$	1 : 0.06	0.6
$(CF_3)_2CF^{\odot}$	1 : 0.02	0.5
$(CF_3)_3C^{\odot}$	1 : 0.005	0.5

The constant values of $2k_\alpha/k_c$ show that the strong preference for attack at the α-position can be attributed to specific hindrance towards attack at the β-position (*i.e.* to the =CHF group).

4.4. Polarity in the Transition State

Convincing evidence for a polarity effect comes from the addition of the methyl and the fluoromethyl radicals to ethylene.

Table 16. Ratio of the rates of addition of methyl and fluoromethyl radicals to ethylene and tetrafluoroethylene at 164 °C [7].

Radical	$k(CF_2=CF_2)/k(CH_2=CH_2)$
$CH_3^{\odot}$	9.5
$CH_2F^{\odot}$	3.4
$CHF_2^{\odot}$	1.1
$CF_3^{\odot}$	0.1

Figure 1 shows that the difference in relative rates of addition is entirely attributable to the difference in the activation energy terms.

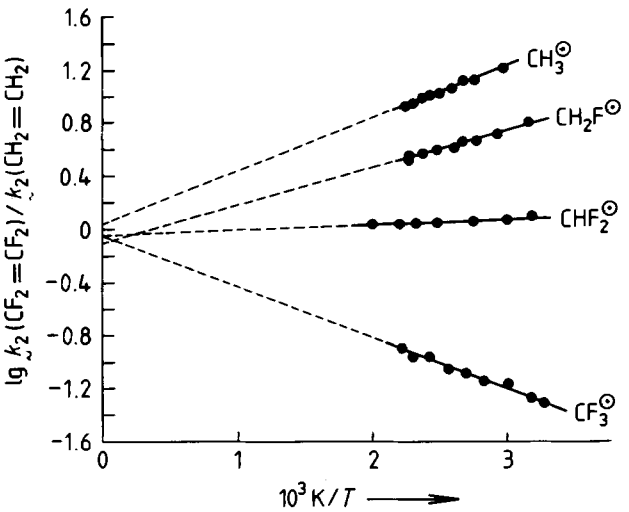


Fig. 1. Arrhenius plots for the relative rates of addition of methyl and fluoromethyl radicals to ethylene and tetrafluoroethylene [7] (see Table 16).

Methyl radicals are thus "nucleophilic" and their rate of addition is accelerated by electronegative substituents in the olefin, while trifluoromethyl radicals are "electrophilic" and their rate of addition is retarded by electronegative substituents. The addition of trifluoromethyl radicals is accelerated by electron—repelling alkyl groups, while attack at the substituted site is progressively inhibited (Table 17).

Table 17. Regioselectivity and rate of addition of trifluoromethyl radicals to olefins at 164 °C.

	$\overset{\alpha}{C}H_2=\overset{\beta}{C}H_2$	$\overset{\alpha}{C}H_2=\overset{\beta}{C}HCH_3$	$\overset{\alpha}{C}H_2=\overset{\beta}{C}(CH_3)_2$
α : β	1 : 1	1 : 0.1	1 : 0.08
$2k_\alpha/k_c$	1	2.3	6.0

4.5. Regiospecificity in Free Radical Addition

The regioselectivity for the addition of trichloromethyl radicals to propene and vinyl fluoride is almost the same, but the rates are very different. The methyl-group substituent enhances the rate of addition of the electrophilic trichloromethyl radical to propene, while the fluorine atom as substituent retards addition to vinyl fluoride. If we now compare the addition of the same radical to trifluoroethylene and 2-chloro-1,1-difluoroethylene, we find the rates of addition are about the same, but that the regioselectivi-

Table 18. Regioselectivity and rate of addition of trichloromethyl radicals to olefins at 164 °C.

	$\overset{\alpha}{C}H_2=\overset{\beta}{C}H-CH_3$	$\overset{\alpha}{C}H_2=\overset{\beta}{C}H-F$	$\overset{\alpha}{C}F_2=\overset{\beta}{C}H-F$	$\overset{\alpha}{C}F_2=\overset{\beta}{C}H-Cl$
$\alpha:\beta$	1:0.07	1:0.08	1:3.5	1:0.04
$2k_\alpha/k_c$	9.0	0.7	0.22	0.21

ties are very different (Table 18). The polar effects of chlorine and fluorine are very similar but the bulk of the chlorine atom is much greater than that of fluorine. These results show that the influence of any substituent must be considered separately in steric and electronegativity terms.

Table 19. Regioselectivity and rate of addition of methyl and fluoromethyl radicals to fluorinated ethylenes [3, 7].

Radical	$\overset{\alpha}{C}H_2=\overset{\beta}{C}HF$		$\overset{\alpha}{C}H_2=\overset{\beta}{C}F_2$		$\overset{\alpha}{C}HF=\overset{\beta}{C}F_2$	
	k/k_c	$\alpha:\beta$	k/k_c	$\alpha:\beta$	k/k_c	$\alpha:\beta$
$CH_3^\odot$	1.1	1:0.2	—	—	5.8	1:2.1
$CH_2F^\odot$	0.4	1:0.3	—	1:0.4	—	1:2.0
$CHF_2^\odot$	0.4	1:0.2	0.1	1:0.1	0.3	1:0.9
$CF_3^\odot$	0.5	1:0.1	0.2	1:0.04	0.05	1:0.5

Table 19 shows the relative rates and regioselectivities of the addition of methyl and fluoromethyl radicals to fluoroethenes. The "nucleophilic" methyl radicals add fastest to trifluoroethylene and the "electrophilic" trifluoromethyl radicals add fastest to monofluoroethylene. All four radicals add preferentially to the unsubstituted end of vinyl fluoride, confirming that the steric effect overrides any polarity influence. Nonetheless, the polar effect is clearly present as shown by the increasing regioselectivity for the addition to 1,1-difluoroethene as the attacking radical becomes more electrophilic. In the addition to trifluoroethylene we find that the polar effect predominates. The "nucleophilic" methyl radicals add preferentially to the CF_2-end of the olefin, whereas the "electrophilic" trifluoromethyl radical adds preferentially to the CHF-end. The total polarity difference between the α- and β-positions in trifluoroethylene is no greater than the difference between the α- and β-positions in vinyl fluoride. However, there is much evidence to show that the steric "hindrance" associated with a CF_2-group is not double that associated with a CHF-group. This means the steric compression involved in forming a new bond at a CF_2-group is also less than twice that involved in forming a new bond at the CHF-group; hence, the polar effect, which is doubled, becomes the predominant factor.

5. Summary of Section 4; Five Rules for Radical Addition Reactions

Free radical addition is a two stage process involving an addition step followed by atom transfer. In all the examples discussed, the overall reaction is assumed to be determined by the initial addition step. The rate expressions can be considered to be comprised of two terms, a preexponential factor (A) and the activation energy (E_A). Just as with the radical transfer reactions, A varies by nearly three orders of magnitude depending on whether an atom or radical is involved; otherwise A varies only slightly, and the major changes in reactivity can be attributed to changes in the activation energy. We can thus reduce the variables which control free radical addition, apart from the relatively small changes in factor (A), to two: the relative strengths of the bonds being broken and formed, and the polarization of the transition state. These are the same factors which govern free radical substitution reactions. The big difference is that addition reactions are reversible and we have, therefore, not included any endothermic reactions. This has meant that the strength of the π-bond broken is relatively (but not entirely) unimportant and the crucial term controlling orientation of addition is the strength of the bond formed. We can summarize the factors which control radical addition by a similar *"Five Rules of Radical Addition"*.

Rule 1

The preferred orientation of addition of a free radical to a monosubstituted olefin will invariably be to the unsubstituted end of the double bond. This can be attributed to the degree of steric compression associated with the formation of the new bond, which overrides other influences on the regioselectivity.

Rule 2

Substituents with CC π-orbitals (e.g. $CH_2=CH-$, C_6H_5-), which can overlap the half-filled atomic orbital of the incipient radical center, enhance the rate of addition at the remote end of the double bond, but vinyl substituents with non-bonding pairs of electrons (e.g. F—, Cl—, CH_3O—) have only a very small "resonance" effect. Most radical additions are exothermic and have early transition states i.e. delocalization of the unpaired electron in the adduct radical is of small importance.

Example: relative rates of addition to butadiene and vinyl chloride (taking ethylene as standard)

$$R^\odot + CH_2=CH-CH=CH_2 \longrightarrow [RCH_2-\overset{\odot}{C}H-CH=CH_2 \longleftrightarrow RCH_2-CH=CH-\overset{\odot}{C}H_2]$$

$$R^\odot + CH_2=CH-Cl \longrightarrow [RCH_2-\overset{\odot}{C}H-Cl \longleftrightarrow RCH_2-\overset{\ominus}{\underset{\cdot\cdot}{C}}H-\overset{\oplus}{Cl}]$$

$R^\odot$	$k(C_4H_6)/k(C_2H_4)$	$k(C_2H_3Cl)/k(C_2H_4)$
$CH_3^\odot$	8.1	4.2
$CF_3^\odot$	20	1.3

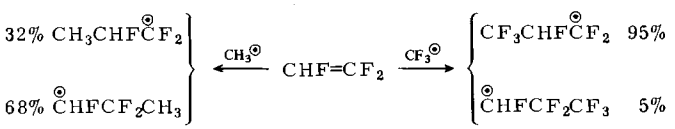
Rule 3

Polarity can have a major effect on the overall rate of addition of radicals to olefins. Methyl radicals behave as "nucleophiles" and their addition is facilitated by electron withdrawing substituents on the olefin, whereas trifluoromethyl radicals behave as "electrophiles", whose addition is retarded by electron withdrawing and assisted by electron repelling substituents.

Rule 4

The regioselectivity of free radical addition to polysubstituted ethenes is controlled principally by the degree of steric compression associated with forming the new bond. If the steric effects are mutually opposed, polarity can be the deciding factor.

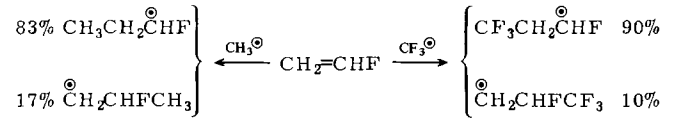
Example: addition of $CH_3^{\odot}$ and $CF_3^{\odot}$ to $CHF{=}CF_2$ at 164 °C.



Rule 5

Even when the regioselectivity of addition to a polysubstituted ethene is determined principally by steric compression, polarity can influence the magnitude of the regioselectivity, making it larger or smaller depending on the relative electronegativity of the radical and the substituents in the olefin. The net effect may be that the more reactive radical is also the more selective.

Example: addition of $CH_3^{\odot}$ and $CF_3^{\odot}$ to vinyl fluoride at 164 °C; the more reactive $CF_3^{\odot}$ radical is also the more selective.



6. Laws of Free Radical Reactions

In addition to the five rules which govern the rate and regiospecificity of free radical substitution reactions we have now proposed five more rules to govern the rate and regioselectivity of free radical addition to olefins. The similarity of the two sets of rules suggests that they are special cases of laws which govern free radical reactions as a whole. This turns out to be the case and we can formulate two laws which comprise all ten rules.

1st Law of Free Radical Reactions (Thermochemistry)

If the heat of reaction ΔH of a free radical process is large and negative, the transition state is early and the reaction will be fast and unselective; if ΔH is large and positive the transition state will be late and the reaction slow and selective; but if ΔH is small (positive or negative) the relative rate and selectivity will depend on other factors, especially polarity.

The relative heats of reaction of free radical processes are largely controlled by the increase (addition reactions) or release (transfer reactions) of steric compression associated with the formation of the incipient radical and by the extent of electron delocalization in the new radical (interactions involving substituents with CC π-orbitals, *e.g.* $CH_2{=}CH{-}$, will have a large effect, but substituents with non-bonding electron pairs, *e.g.* $CH_3O{-}$, only have a small effect). The effects of steric compression and electron delocalization are only fully manifest in a late transition state.

2nd Law of Free Radical Reactions (Polarity)

Polarity, i.e. the difference in relative electronegativity, cannot be completely separated from bond dissociation energies, but dipole-dipole interactions, i.e. opposing or complementing electrostatic forces, in the transition state can substantially raise or lower the energy barrier in both radical substitution and radical addition reactions.

These polar forces can be manifest quite early in a reaction (*i.e.* polarity is important in both exothermic and endothermic reactions), and in cases where ΔH is small (positive or negative) this means that the more reactive radical can also be the most selective.

7. Conclusions and Outlook

The purpose of proposing "rules" and "laws" serves to summarize a very wide collection of empirical data in a concise and coherent form. The "laws" are also applicable to homolytic dissociation reactions, *i.e.* those involving the rupture of a single bond to form two radicals. It seems likely that the "laws" will also apply to radical dimerizations, although as yet there is insufficient data available about the dimerization of very bulky radicals. (The heat of reaction of dimerization of small radicals is large and negative and hence, according to the first law, the reactions are fast and unselective.)

The second purpose in proposing "rules" and "laws" is to stimulate further research aimed at verifying or disproving these laws. It is to be hoped that the rules will also stimulate theoretical studies. The concepts used in formulating the rules and laws will appear in a different guise in any sophisticated theoretical treatment. Nonetheless steric compression and dipole-dipole interactions will be inherent in any comprehensive theoretical treatment. The simple qualitative ideas used here cannot be expected to completely account for small differences in rate or regioselectivity. For example, 1,1-difluoroethene is particularly unreactive towards radicals due to a high π-bond dissociation energy, which cannot be explained in our qualitative picture. Similarly over-simplified theoretical treatments (*e.g.* "extended Hückel" calculations) are even less comprehensive, and for example do not account for the destabilization attributable to steric compression. Full calculations will eventually render the use of rules and laws less necessary. However, there will always be a need for qualitative treatments summarizing empirical data and which are consistent with sophisticated theoretical ideas; it is to be hoped that this review article will provide the basis for such a treatment.

This article is based on a lecture delivered at the 3rd International Symposium on Organic Free Radicals at Freiburg (September 1981); the author was able to acknowledge some of the many organic chemists on whose work the proposed "rules" were based. The importance of polarity in radical transfer was developed particularly by Walling, Russell, and Minisci; the importance of steric effects was emphasized by Rüchardt, and in a very different way by Beckwith; factors controlling addition were thoroughly studied by Haszeldine and the problem of selectivity was recognized by Giese. At

the Symposium further examples of the importance of steric effects (E. Vismara) and polar effects (P. Boldt) were given. The author hopes that those not specifically mentioned above will accept this general acknowledgment. He must however acknowledge his own colleagues and in particular J. C. Walton.

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New Possible Applications of Heavy Main-Group Elements in Organic Synthesis**

New synthetic methods (36)

By Thomas Kauffmann*

Dedicated to Professor Leopold Horner on the occasion of his 70th birthday

Aside from elements of the 2nd row, and one element of the 3rd row of the periodic system—Si, P, S, and Se, respectively, whose organoelement groups such as Me_3Si and $Ph_3P^{\oplus}$ have proven useful in numerous organic syntheses—other elements of the 3rd as well as 4th and 5th row (Ge, As, Sn, Sb, Te, Pb, Bi) can also be used as components of synthetically useful organoelement groups, the elements As, Sn, and Pb, in particular, offering certain advantages over the others. Some of these organoelement groups are suitable equivalents for Li- or halogen-substituents attached to carbon; they stabilize carbanionic centers (minimum of this effect at the 3rd-row elements), and owing to their suitability as leaving groups in β-eliminations, also open up interesting synthetic possibilities. The thermally induced *syn*- and silica-gel induced *anti*-elimination of Ph_3Sn, Ph_2Sb, Ph_3Pb, together with β-OH, are novel. With the newly synthesized compounds $Ph_nEl—CH_2—Li$ (El = Sn, Pb, As, Sb, Bi) and other α- and β-lithiated R_nEl- and $Ph_2As(O)$-reagents such organoelement groups can be introduced into organic compounds and exploited in organic and organoelement syntheses.

1. Organoelement Functional Groups

Organic chemistry largely concerns the chemistry of functional groups. More and more "organoelement functional groups"[2] containing elements previously not considered by the organic chemist are presently acquiring importance in organic synthesis. There are some groups of this type whose central atom is a transition metal (examples: 3rd row in Scheme 1); however, groups with a main group element are presently of much more importance: for instance, regarding hydroboration, Wittig reaction, organoselenium reagents. Unlike classical functional groups such as —OH, $—NH_2$, —CO—, —COOH, the organoelement functional groups are cleaved off again during the course of the synthesis. The designation "mobile functional groups"[3], however, would raise objections in that such a designation frequently also holds for the classical functional groups Cl—, Br—, I—.

HO—	H_2N—	—CO—	Hal—	
R_2B—	Me_3Si—	$Ph_3\overset{\oplus}{P}$—	$Me_2\overset{\oplus}{S}$—	RSe—
$RC\overset{\ominus}{u}$—	$(CO)_3Cr$—	$(C_5H_5)_2ClZr$—		

Scheme 1. Examples of classical functional groups and organoelement functional groups.

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[**] New Reagents, Part 24.—Part 23: [83]; 7th Summary Progress Report on Organic Anionochemistry.—Earlier Progress Reports: [1].

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Main group elements that have proven particularly useful as constituents of novel functional groups are to be found in the region of the periodic system shown in Scheme 2. Hitherto, their use has almost been restricted to the light elements B, Si, P, S, and Se; only Sn (see Section 2.1) constitutes an exception. This prompted the question as to what extent the heavier elements Ge, As, Sb, Te, Pb, and Bi are suitable[4] as constituents of new functional groups.

In general, we examined compounds with singly-bonded groups of the type Ph_nEl-, which are less volatile and so presumably less poisonous than their Alk_nEl-analogues. Such groups can be replaced by Li-, halogen-, or H-atoms; they are electron-withdrawing, and some can be readily eliminated together with a β-O- or β-H-atom. The attractiveness of these groups largely lies in the fact that-with limitations in the case of P, Bi, Te-the C—El bond is just as stable as a C—N, C—O or C—Hal bond towards H_2O and O_2. Hence, when using them the organic chemist can keep to conventional methods and apparatus.

(B)			
	(Si)	(P)	(S)
	Ge	As	(Se)
	(Sn)	Sb	Te
	Pb	Bi	

Scheme 2. The main group elements so far frequently used in organoelement groups are circled.

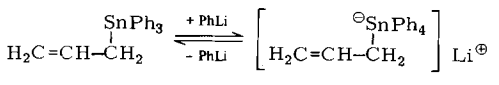
Our interest in organoelement functional groups was awakened when it was shown that the scope of application of 1,3-anionic cycloadditions[5] can be considerably extended by cleavable electron-withdrawing organoelement groups (see Section 4.2.2).

2. Organoelement Groups as Li-Equivalent

2.1. Organoelement/Li Exchange

The activation of C-atoms by Li-substituents enables the coupling of a large variety of electrophilic moieties. Aside from H/Li exchange, the most important method for introduction of Li into organic compounds is by halogen/Li exchange—which permits carbanionic centers to be generated at sites where this is impossible by H/Li exchange owing to relatively low CH-acidity.

The third possibility, namely "organoelement/Li exchange"[6], is much less known[7]. Of these reactions, in which the intermediary occurrence of ate-complexes is rarely questionable[8], *Seyferth et al.*[9] have mainly used stannyl/Li exchange on a preparative scale, *e.g.* for the very convenient synthesis of allyllithium compounds (Scheme 3)[9].



Scheme 3.

The possibilities offered by seleno/Li exchange have been exploited, in particular, by *Seebach et al.*[10] and by *Krief et al.*[11].

The following features are common to both halogen/Li and organoelement/Li exchange: a) The reactions usually proceed rapidly, even below −50 °C. b) Since equilibria are established, good yields are achieved only when the negative charge in the organolithium compound that is formed is stabilized better than in the Li-reagent (exceptions: shift in equilibrium, *e.g.* precipitation of a sparingly soluble product). c) With the exception of boron (sextet → octet on formation of the ate-complex), the exchange takes place only in the case of elements having valence electron shells that can be expanded to a decet; *the exchange takes place markedly easier with 4th- and 5th-row elements than with 2nd- and 3rd-row elements.*

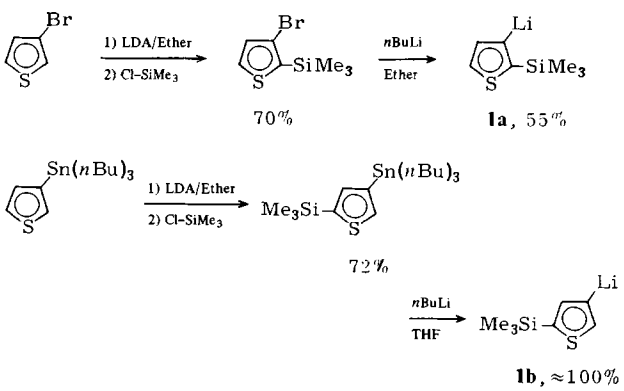
Organoelement/Li exchange has the advantage that at least nine elements (Scheme 4) can be conveniently used, as opposed to only two elements in the case of halogen/Li exchange (Cl is very seldom suitable).

A					B
	B				(Cl)
			(As)	Se	Br
		Sn	Sb	Te	I
Hg	Tl	Pb	Bi		

Scheme 4. Elements suitable for organoelement/Li (A) and halogen/Li-exchange (B).

A further advantage is that a reactive, and, in the case of stannyl- and plumbyl-groups, coordinatively saturated compound *e.g.* tetraphenylstannane (Scheme 3) is usually formed as by-product. Therefore, other than in the case of halogen/Li exchange, which leads to alkyl or aryl halides, undesirable secondary reactions of the lithiated product (see Section 2.2.2) are rarely encountered.

All the elements amenable to organoelement/Li exchange are less electronegative than the halogens Cl, Br, and I. Scheme 5 shows how this can be favorably exploited: Whereas H/Li exchange with the Li-equivalent Br— (1st reaction step) takes place at the 2-position of the thiophene, the Li-equivalent *n*-Bu_3Sn directs the Li into the 5-position, resulting in the isomer **1b** being formed instead of **1a**[12]. This reaction could have wider synthetic utility.



Scheme 5. All reactions at −60 °C [12]; LDA = lithium diisopropylamide, THF = tetrahydrofuran.

A further reason for organoelement/Li exchange being preferred over halogen/Li exchange could lie in the better accessibility of organoelement educts. This holds true, *e.g.*, for some of the compounds $(Ph_nEl)_2CH_2$ **3** dealt with in Section 2.2.

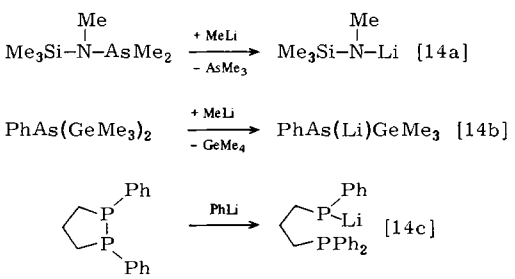
As expected, the suitability of an organoelement group for organoelement/Li exchange strongly depends on the electronegativity of the site of attachment: for example, a Ph_2As group attached to an sp^3 or sp^2 C-atom can be replaced by Li only with difficulty, whereas arsino/Li exchange takes place rapidly, even at 0 °C, in the case of the arsinoethynes **2** (Scheme 6)[13]; this is also of preparative interest because of the thermal instability of stannyl- or plumbylethynes and the much higher thermal stability of arsinoethynes.

$$\underset{\mathbf{2}}{Ph_2As{-}{\equiv}{-}G} \xrightarrow[0\,^\circ C,\ THF]{n\text{BuLi}} \underset{\approx 100\%}{Li{-}{\equiv}{-}G}$$

Scheme 6. G = $AsPh_2$, $SiMe_3$ [13].

Finally, it should be mentioned that organoelement/Li exchange is not just restricted to *C*-bonded organoelement groups: whereas groups such as R_3Si—, R_3Ge—, and R_2P—, which attach to carbon are not as a rule amenable to this exchange, they can be exchanged if they are attached to a relatively electrophilic heteroatom (examples: Scheme 7).

Regarding the *stereochemistry* it was established that stannyl/Li exchange at vinyl compounds takes place with complete retention of configuration[15], which could recently be demonstrated also for the exchange at an sp^3 C-atom in the synthesis of an α-lithiated ether[16].



Scheme 7. Organoelement/Li exchange at heteroatoms.

Organoelement/Li exchange offers still further inexhaustible possibilities. Some of these are outlined in the following Sections.

2.2. Organoelement/Li Exchange at G_2CH_2

2.2.1. Synthesis of G—CH_2—Li by Organoelement/Li and, for Comparison, by Halogen/Li Exchange

To the reagents which have proven useful in organic synthesis belong anions of the type G—$CH_2^{\ominus}$, where G (as throughout this review) symbolizes an organoelement group. Some of these reagents have been synthesized in the form of compounds G—CH_2—Li **4** by organoelement/Li exchange from disubstituted methanes **3** (G = PhSe, PhTe[10, 17]), or G—CH_2—G′ **10** (*e.g.* G = PhS—, G′ = PhSe—[11b]).

We checked whether the methyllithium derivatives **4** listed in Table 1 are accessible by organoelement/Li exchange (Scheme 8) from the symmetrically disubstituted methanes **3**, which, with exception of the Bi-compound **3f**[18, 24n], were all well known[*].

$$\underset{}{Hal_2CH_2} \xrightarrow{2\,M\text{-}G} \underset{\mathbf{3}}{G_2CH_2} \xrightarrow{RLi} \underset{\mathbf{4}}{G{-}CH_2{-}Li}$$

Scheme 8. M = Li, Na, K.

Table 1. Synthesis of G—CH_2—Li **4** from **3** by organoelement/Li exchange in THF according to Scheme 8.

	G	RLi	**4**, Yield [%]
a	Ph_3Ge	*n*BuLi or PhLi	0 [a, c] [23f]
b	Ph_3Sn	PhLi	36 [a], 52 [b] [24n, e]
c	Ph_3Pb	PhLi	89 [a], 100 [b] [24m, n]
d	Ph_2As	*n*BuLi	72 [c] [23d, 25a]
e	Ph_2Sb	PhLi	100 [a] [25b]
f	Ph_2Bi	PhLi	70 [a] [24n]

Molar ratios: [a] **3** : PhLi = 1 : 1; [b] **3** : PhLi = 1 : 1.5; [c] **3** : *n*BuLi = 1 : 4.

The synthesis of **4b** and **4c** appeared particularly problematical, since it was not expected that the electropositive, heavy elements Sn and Pb would stabilize a carbanionic center. Moreover, secondary reactions were expected to take place. Some stannyl- and plumbylmethyllithium derivatives had indeed already been described in the literature, but they were of type **5**, with carbanion-stabilizing substituents Z and Z′.

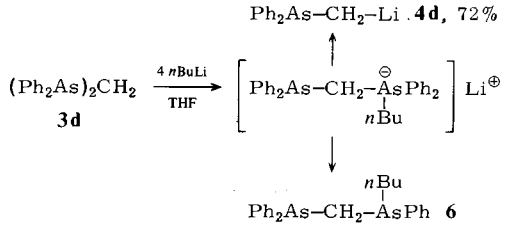
$$R_3El{-}\overset{\displaystyle Z}{\underset{\displaystyle Z'}{C}}{-}Li$$

5, El = Sn, Pb

Z = Z′ = Hal [19]
Z = Z′ = SR′ [20a, b]
Z = Z′ = $B(OR')_2$ [21]
Z = SMe, Z′ = $SiMe_3$ [20c]

More interesting in this connection was the synthesis of PhTe—CH_2—Li **4h** by phenyltelluro/Li exchange (yield ≈ 100%) described by *Seebach et al.*[17]; Te is, of course, markedly more electronegative than Sn and Pb.

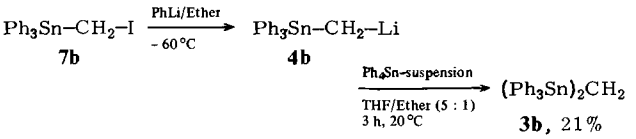
With exception of **4a** the desired methyllithium derivatives **4** are formed in preparatively satisfactory yields (Table 1)[2, 4, 22]. Whereas PhLi could generally be used—in which formation of a mixture cannot occur by ligand exchange—the more reactive *n*BuLi was required in excess for the synthesis of **4d**. Small amounts of **6** are formed by ligand exchange *via* an ate-complex (Scheme 9).



Scheme 9. [23d, 25a].

[*] In compounds **3**, **4**, **7**, **12**, **13**, **34**, **35**, **57** with G = Ph_nEl, **a** means: Ph_nEl = Ph_3Ge, **b**: Ph_3Sn, **c**: Ph_3Pb, **d**: Ph_2As, **e**: Ph_2Sb, **f**: Ph_2Bi, **g**: PhSe, **h**: PhTe.

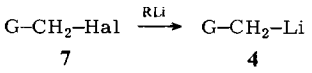
The reaction **3b→4b** was examined more closely: Demonstration of the back reaction shown in Scheme 10 reveals that, as expected, an equilibrium is set up[24e]. Accordingly, the yield of **4b** can be increased by increasing the concentration of PhLi (Table 1). The reaction analogous to **4b→3b** (Scheme 10) using Pb instead of Sn could likewise be demonstrated (yield 19%)[24m].



7b **4b** **3b**, 21%

Scheme 10. [24e].

For comparison, the methyllithium derivatives **4** were also synthesized from halogen compounds **7** by halogen/Li exchange[2,4,26] (Table 2). With exception of **4a**[27], none of the compounds **4** in Tables 1 and 2 had hitherto been described in the literature.



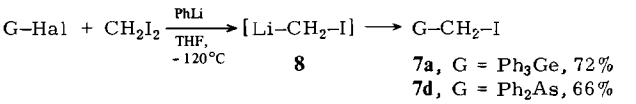
7 **4**

Table 2. Synthesis of G—CH_2—Li **4** from **7** by Hal/Li exchange.

	G	4, Yield [%]
a	Ph_3Ge	≈ 100 [a, b] [23f]
b	Ph_3Sn	98 [a] [24k], 86 [b] [24e]
c	Ph_3Pb	≈ 70 [a] [24k], ≈ 100 [b] [24m]
d	Ph_2As	≈ 100 [a, b] [24i]
i	Me_3Sn	92 [a] [24k]
j	$(n-Bu)_3Sn$	≈ 100 [a] [24k]

[a] In ether, molar ratio **7** : *n*BuLi = 1 : 1; [b] in THF, **7** : PhLi = 1 : 1.

Educts **7a** and **7d** were synthesized by using the reagent **8**, which is stable for only a short time at −100 °C (Scheme 11). The trick[24j] for achieving good yields is to add the organoelement halide at the same time as the CH_2I_2, and not later[28].—The rest of the halides **7** (Table 2) are accessible by means of the Simmons-Smith reagent[29], whose nucleophilicity is inadequate for the synthesis of **7a** and **7c**.

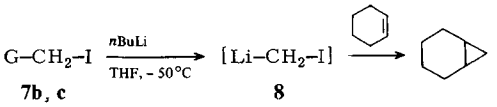


8

7a, G = Ph_3Ge, 72%
7d, G = Ph_2As, 66%

Scheme 11. CH_2Br_2 can also be used instead of CH_2I_2 [24j].

Since the lithium compounds **4** are distinctly more reactive in THF than in ether (see Section 2.2.2), they were also prepared by halogen/Li exchange with PhLi in THF (Table 2). By way of contrast, *n*BuLi in THF proved to be unsuitable in the cases investigated (Scheme 12), since competing organoelement/Li exchange takes place: After addition of cyclohexene, norcarane could be detected, thus indicating that the reaction follows the course formulated in Scheme 12[24e].



7b, c **8**

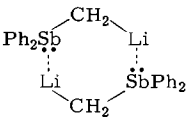
Scheme 12. Yield of norcarane in the case of **7b**, G = Ph_3Sn, 28%, in the case of **7c**, G = Ph_3Pb, 49% [24e].

In contrast to most of the organoelement/Li exchange reactions listed in Table 1[30], no sparingly soluble product separates out in the reactions given in Table 2, *i.e.* establishment of equilibrium is not disturbed. From these reactions, therefore, it can be concluded that the relatively electropositive, heavy main-group elements Sn, Pb, As, Sb, Bi readily stabilize a neighboring carbanionic center; this was confirmed by H/Li exchange reactions (see Section 4.1). Experiments with the tri*alkyl*stannyl compounds **7i** and **7j** (Table 2) show that phenyl ligands on the element are not decisive for this stabilization.

The reagents **4** synthesized can be used for indirect nucleophilic lithio- (El = Sn, Pb, Sb; Section 2.2.3) and halomethylation (El = As, Sb, Bi; Section 3.3.1) and for carbonyl olefination (El = Ge, Sn, Pb, Sb; Section 5.1.1).

2.2.2. *Stability and Reactivity of G—CH_2—Li*

Seebach and *Beck*[17] were surprised at the stability of the phenyltelluromethyllithium **4h** which they synthesized (no decomposition after 24 h in THF at 0 °C under inert gas). Triphenylstannyl- **4b**, triphenylplumbyl- **4c**, diphenylarsino- **4d**, and diphenylstibino-methyllithium **4e** are likewise astonishingly stable: **4b** (in ether) or **4c-e** (in THF) could still be detected to the extent of 20, 17, 100 and 96%, respectively, after 24 h at 20 °C[24k,h]. Free electron pairs on the heteroatom would thus appear to effect additional stabilization (cf. *e.g.* **9**). However, the Bi-compound decomposes relatively rapidly in THF at ≈20 °C; only ≈20% was still detectable after 30 min[24i].



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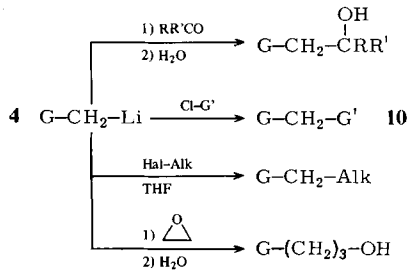
4a—f[2,4,26,31,24e,h-k,m,n] and **4h**[17,24a] react with aldehydes, ketones (see Table 10), organoelement halides, and—as far as tested—with oxiranes in moderate to good yields according to Scheme 13[32].



Scheme 13 (see also Tables 3 and 10).

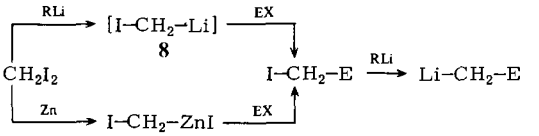
Reactions with alkyl halides proved more critical: As a rule, only **4a** undergoes reaction in ether; in THF, on the other hand, use of **4a-d** leads to CC-coupling in prepara-

Table 3. Synthesis of G—CH_2—Alk from **4** and alkyl halides in THF at −30 to +20 °C. Yields based on **4**.

	G	Hal—Alk	Yield [%] [a]	[b]
4a	Ph_3Ge [24j]	Iodomethane	92	(34)
		Iodoethane	85	46 (35)
		1-Iodopropane	86	
		1-Iodobutane	86	
4b	Ph_3Sn [24e]	1-Iodopropane	75	
		1-Iodobutane		72
		1-Iodopentane	78	
4c	Ph_3Pb [24m]	Iodomethane	68	67
		Bromoethane	69	
		1-Iodobutane	89	
		Benzyl bromide	19	
4d	Ph_2As [24i, 25a, 31]	1-Iodopropane	93	30
		1-Brombutane	85	2
		1-Bromoctane	57	0
		1-Iodobutane		48
4e	Ph_2Sb [26, 31]	1-Iodopropane	15	
		1-Brompropane	12	

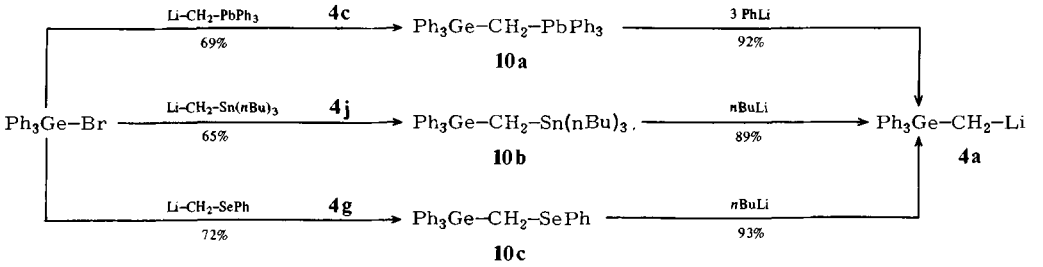
[a] **4** prepared by organoelement/Li exchange (in the case of **4a** see Section 2.2.3). [b] **4** generated by bromine/Li (values in brackets) or iodine/Li exchange.

and the analogous Br-compound (extensive decomposition even after a few minutes at −100 °C) (Scheme 15) is very limited, despite the variant involving generation of the halomethyllithium immediately in the presence of the electrophile (see Scheme 11) indicating a potential improvement in this connection. Moreover, possible indirect lithiomethylation with the Simmons-Smith reagent in the case of strong electrophiles (*e.g.* Ph_3SnCl[29]) (Scheme 15) also fails, even with compounds like Ph_3SiCl or Ph_3GeBr[24j].



Scheme 15. EX = electrophile.

A favorable extension to the methodology is provided by organoelement/Li exchange: Like PhSe—CH_2—Li **4g**[10], the new reagents **4b**, **4c**, **4j**, and—to a lesser degree—**4e** can also be used for nucleophilic lithiomethylation (Schemes 16 and 17). Of importance is that these compounds are thermally considerably more stable than bromomethyllithium or **8** (see Section 2.2.2). Compared to **10a** and **10c** the intermediate **10b** has the disadvantage of not being crystalline. Disadvantageous in the case of **10a** is that 2—3 moles of PhLi are required per mole of educt for the organoelement/Li exchange.

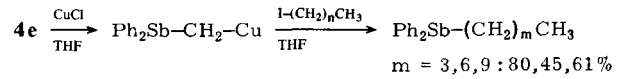


Scheme 16 [24j].

tively satisfactory yields (Table 3). **4e**, **4f**, and **4h** (G = Ph_2Sb, Ph_2Bi and PhTe, respectively), however, also react only slowly or not at all (**4e**) in THF. This would suggest that these compounds form stable, less reactive aggregates of type **9** with participation of the free electron pairs.

As follows from Table 3, the method adopted for the synthesis of the reagent **4** also influences the yields of the products obtained in its reactions with alkyl halides: The halobenzene formed as byproduct during synthesis of **4** by halogen/Li exchange with PhLi deactivates the reagent **4** by complexation, while the by-product *n*-butyl halide can undergo CC-coupling with **4**.

The very moderate yields obtained on reaction of **4e** to give alkyl(diphenyl)antimony could be noticeably increased by transmetalation to the copper(I) compound (Scheme 14)[24,31].

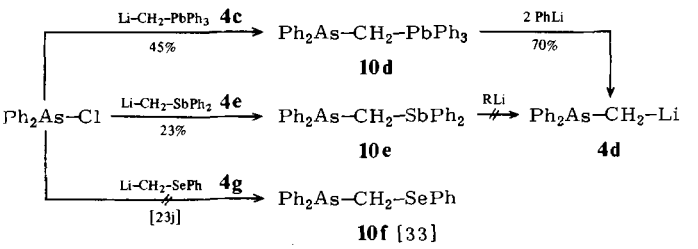


Scheme 14. [24h, 31].

2.2.3. *Indirect Nucleophilic Lithiomethylation with G—CH_2—Li*

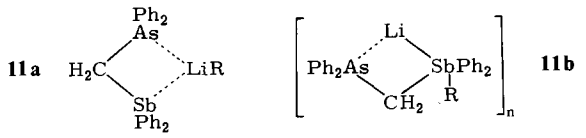
The possibility of carrying out indirect lithiomethylations with the extremely thermolabile iodomethyllithium **8**

Free electron pairs on the heteroatoms of reagent and educt can have an unfavorable effect in such reactions, as shown in Scheme 17: Although PhLi reacts smoothly with methylenebis(diphenylstibane) **3e** with organoelement/Li exchange (Table 1), the analogous compound **10e** can be quantitatively recovered after reaction with PhLi or *n*BuLi and hydrolysis with water[24b].



Scheme 17 [24b].

Either LiR is deactivated by complexation in accordance with **11a**, or an aggregated energy-deficient ate-complex is formed, *e.g.* **11b**, which yields the educt again during the hydrolysis.

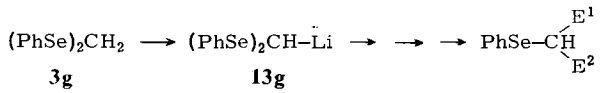


11a **11b**

2.3. Organoelement/Li Exchange at G_3CH

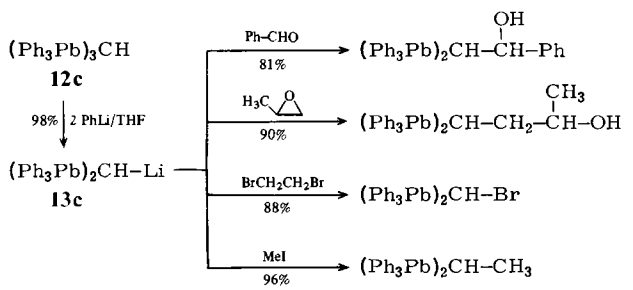
2.3.1. Bis(triphenylplumbyl)methyllithium

Numerous organoselenium compounds can be synthesized from **3g** by H/Li exchange to give **13g**, reaction with an electrophile, seleno/Li exchange, and renewed reaction with an electrophile (Scheme 18)[10,11].



Scheme 18.

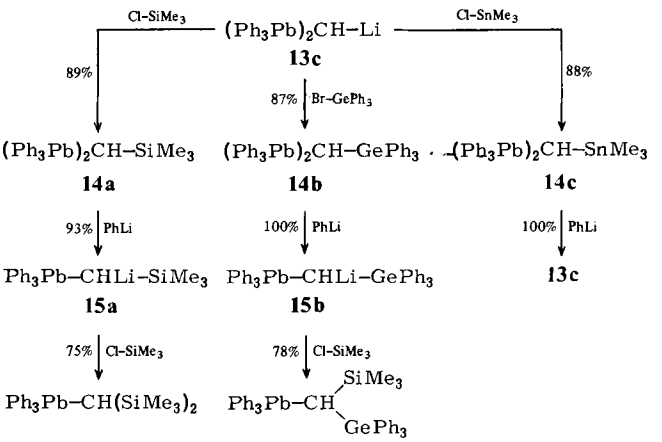
The compounds $(Ph_nEl)_2CH_2$ (El = Sn, Pb, As, Sb) **3b—e** can also be lithiated by H/Li exchange to **13b—e**, but only under conditions which lead to strongly deactivated Li-compounds (see Section 4.1.1). In the case of **3c**, El = Pb, this difficulty could be overcome by using organoelement/Li exchange on a compound of the type G_3CH **12**: The well-known tris(triphenylplumbyl)methane **12c**, which can be conveniently prepared from chloroform and Ph_3Pb—Li[34], and whose yield could be increased from 66 to 91%[23h], reacts quantitatively with PhLi to give **13c**[35], which proved to be surprisingly stable (45—50% still existing after 5 h in boiling THF) and to be very versatile, owing to its exceptional reactivity and selectivity and its exchangeable plumbyl groups (see Schemes 19, 20): On reaction with non-enolizable aldehydes and ketones[36] it forms β-hydroxybis(plumbyl)compounds (57—81%)[24m], which can be decomposed to plumbyl- and lithio-alkenes (see Section 5.1.3). Primary alkyl halides (secondary and tertiary do not react) are converted into alkylidenebis(plumbanes) (25—96%)[24m], from which α-plumbylalkyllithium compounds can be prepared (see Section 5.1.4).



Scheme 19 [24m].

13c reacts with organoelement halides to give derivatives **14**, which contain a further organoelement group besides two plumbyl groups and which can be decomposed to a daughter generation of Li-reagents **15** containing only one plumbyl group, also replaceable by Li (examples: Scheme 20[24,35]). Isolation of the pure product is, as a rule, easy, since plumbyl compounds very readily crystallize. A disadvantage is that plumbyl/Li exchange usually requires 2 moles of PhLi per mole of **14**, which in turn necessitates the use of 2 moles of electrophile in subsequent reactions.

On reaction with PhLi, the tri*methyl*stannyl compound **14c** exchanges exclusively the trimethylstannyl group for Li. In the corresponding triphenyl compound, on the other hand, exchange of all three groups takes place to the same extent[24m].

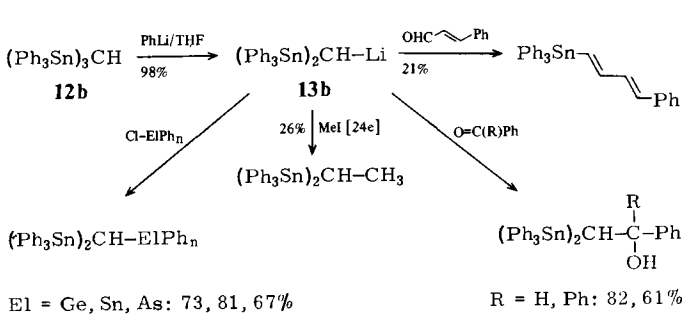


Scheme 20. Use of **15a**: Scheme 61 [24].

$(PH_3Pb)_4C$ is not attacked by LiR (R = Me, *n*Bu, Ph)[25c].

2.3.2. Bis(triphenylstannyl)methyllithium

Other than quoted in the literature[37], the heteroanalogue tris(triphenylstannyl)methane **12b** of **12c** is currently only available by an involved synthesis (see Section 4.1.1). The Li-compound **13b**, which is obtainable in almost quantitative yield from **12b**, is a promising educt, but very few reactions have been tried out (Scheme 21)[23e].



El = Ge, Sn, As: 73, 81, 67%

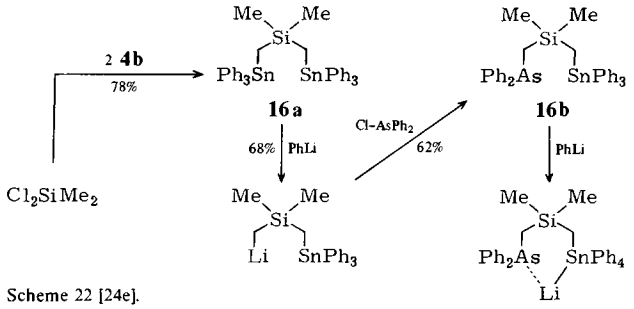
R = H, Ph: 82, 61%

Scheme 21 [23e].

2.4. Compounds of Type G—CH_2—G′—CH_2—G

Compounds of type **16** would be convenient educts for the synthesis of more complex organoelement molecules, if they would allow the peripheral groups to be exchanged for Li without the central group being attacked. However,

preliminary investigations (Scheme 22) have shown that limitations are soon encountered. Though **16a** could be relatively easily lithiated, further reaction in preparatively satisfactory yield was possible only with Ph_2AsCl, and the product **16b** did not undergo stannyl/Li exchange (almost quantitative recovery after addition of water). Presumably the resulting ate-complex is stabilized to such an extent by the diphenylarsino group that $SnPh_4$ is not eliminated[24e].

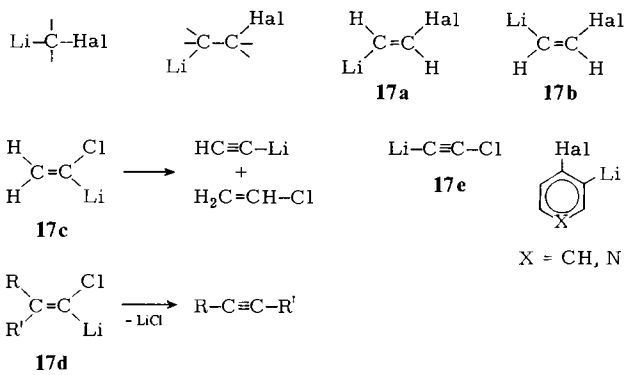


Scheme 22 [24e].

3. Organoelement Groups as Halogen Equivalents

3.1. Motivation and Previous Uses

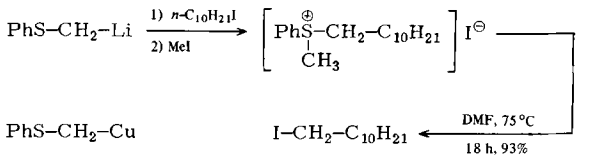
Halogen substituents are important functional groups, since they can be readily exchanged, often stereospecifically, for other functional groups and C- and metal-atoms. However, there are limits to their use, in that a negative charge in the α- or β-position to the halogen has a strong destabilizing effect. Thus, the groups and compounds depicted in Scheme 23 can be used as nucleophiles only at very low temperatures, if at all[38]. **17e** is explosive.



Scheme 23.

It is meaningful, therefore, to search for equivalents for *C*-bonded halogens. These equivalents should, first of all, tolerate a neighboring negative charge or partial charge, and, moreover, be strongly nucleophilic.

Corey et al.[39] were the first to use methylmetal reagents (Li, Cu) containing an organoelement group (= PhS) as halogen-equivalents for nucleophilic halomethylations. Disadvantages of their method (Scheme 24) are long reaction times, limitation to introduction of iodine, and, above all, that practically only alkyl halides can be used as substrates. If instead phenylthiomethyllithium is allowed to react with aldehydes, ketones or oxiranes, then the hydroxy group of the product in the "onium cleavage" with MeI/NaI is, according to our observations[25a], partially methylated.



Scheme 24 [39]. "Onium Cleavage".

Krief et al.[40] carried out analogous but more rapid reactions with the Se compound **4g** and also described indirect nucleophilic α-bromoalkylations with Se reagents (see Section 3.3.2). *Brown et al.*[41] likewise used an organoelement group as halogen-equivalent in the indirect anti-Markownikoff addition of HHal to olefins *via* borane addition and halogenolysis. The same can be achieved by hydrozirconation and subsequent halogenolysis at 0 °C[42].

3.2. Organoelement/Halogen Exchange at C-Atoms

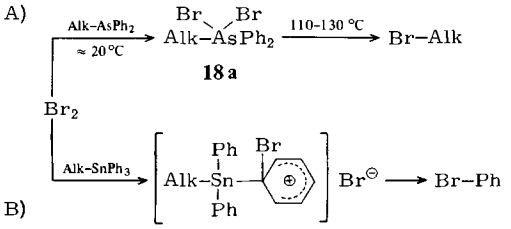
Prerequisites for the use of halogen equivalents in organic synthesis are easy introduction of the equivalent and favorable exchange of halogen. Should organoelement groups function as halogen substitutes in carbanionic reagents, high thermostability and nucleophilicity of these anions is also desirable.

As a rule, the coupling of organoelement groups with C-atoms is unproblematical, since both nucleophilic as well as electrophilic introduction is possible. Moreover, on using suitable organoelement groups (see Sections 2.2.2; 2.3.1; 3.3.1—3.3.3) carbanions exhibiting satisfactory stability and nucleophilicity can be generated. However, difficulties are encountered on exchange of the organoelement group for halogen.

3.2.1. Alkyl-Bound Organoelement Groups

Since halogens attached to sp^3 C-atoms are generally far more versatile than those attached to sp^2 or sp C-atoms there is mainly a demand for equivalents for alkyl-bound halogen. In the case of the organoelement groups which represent potential candidates for this purpose, exchange for halogen is most difficult if the group is attached to a *primary* sp^3 C-atom.

The disadvantages of the "onium cleavage" used by *Corey*[39] and *Krief*[40] were pointed out in section 3.1. "Halogenolysis" with halogen or SO_2Cl_2 might as a rule be more favorable (example: Scheme 26). As in the "onium cleavage", an element with a free pair of electrons is also required. The electrophilic attack of the halogen leads in these cases to "dihalides" such as **18a** (Scheme 25A),



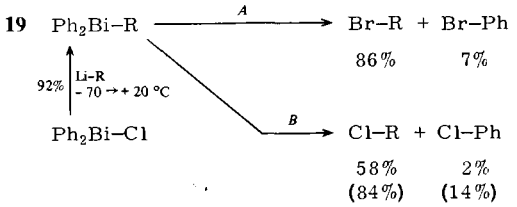
Scheme 25.

which eliminate alkyl halides on heating. The remaining valences of the element (as *e.g.* in the diphenylarsino group) are more appropriately blocked with phenyl ligands, which do not participate in the exchange reactions.

If the central atom of the organoelement group does not bear a free electron pair, all the alkyl moieties participate in the exchange reactions, or the halogen initially attacks a phenyl ligand (if present), which leads to undesirable cleavage of this moiety (Scheme 25 B). Such groups are thus unsuitable as halogen-equivalents on sp^3 C-atoms.

The formation of alkyl halides by halogenolysis of organo-arsenic, -antimony, and -selenium compounds is already well known[43]. But this approach has only recently been used for the directed synthesis of *primary* alkyl halides, while *Krief et al.*[40] had already previously synthesized *secondary* and *tertiary* alkyl halides by productive halogenolyses of organoselenium compounds.

Alkyldiphenylbismuthanes such as **19**, and thus also their halogenolysis, were previously unknown. We synthe-

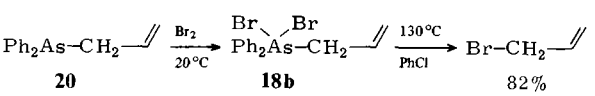


Scheme 26 [18, 24n]; R = *n*-C_5H_{11}. *A*: Br_2, ether −70→+20 °C; *B*: analogous to *A* with SO_2Cl_2 or with Cl_2/THF, 0 °C.

sized them according to Scheme 26—the stratagem here being the use of alkyllithium compounds at low temperatures instead of Grignard compounds at elevated temperatures[43a]—and found that bromolysis and chlorolysis already take place below 0 °C (Scheme 26).

Table 4 enables a comparison of the methods and groups for organoelement/Br and organoelement/I exchange at a primary sp^3 C-atom. On bromolysis, Ph_2As and Ph_2Bi give the highest yields; the air-sensitive group Ph_2Bi is only used at low exchange temperatures. In the "onium cleavage" the yields with PhS, PhSe, PhTe are more favorable than with Ph_2As and Ph_2Sb; surprisingly, however, the lowest exchange temperature was with Ph_2Sb.

In the bromolysis of allyldiphenylarsane **20** with bromine in the molar ratio 1:1 the CC bond remains intact (Scheme 27), while in the case of cyclopropyldiphenylarsane the exchange is accompanied by ring opening[4, 23g].



Scheme 27 [4, 23g].

Organoelement/halogen exchange by halogenolysis at *secondary and tertiary sp^3 C-atoms* is unproblematical. When attached to such C-atoms the otherwise unfavorable PhSe and PhTe groups can be exchanged for bromine already at room temperature in moderate to good yields; on the other hand, "onium cleavage" fails in this case[40]. On using Ph_2As, halogenolysis with Br_2 or I_2 is practically quantitative but requires a temperature of 110—130 °C.

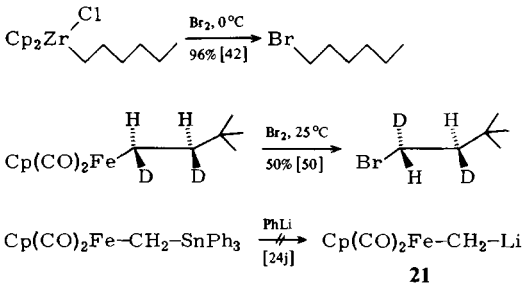
Table 4. Synthesis of *n*-$C_6H_{13}Br$ by bromolysis of *n*-$C_6H_{13}G$ with Br_2 and of *n*-$C_6H_{13}I$ by "onium cleavage" of *n*-$C_6H_{13}G$ with MeI/NaI. Cleavage temperatures and yields.

G	*n*-$C_6H_{13}Br$		*n*-$C_6H_{13}I$	
	T [°C]	Yield [%]	*T* [°C]	Yield [%]
Ph_2As	130	86 [46, 47]	20	<3 [25a]
Ph_2Sb	220	65 [24h, 25b]	20	41 [25b] [a]
Ph_2Bi	−10	84 [24n, 18]		
PhS			80	93 [39]
PhSe	80	44 [23a, 46]	80	80 [40]
PhTe	80	27 [24a]	66	77 [24a]

[a] Since methylation with MeI was not possible, ethylation was carried out with $[Et_3O]BF_4$.

To our knowledge the only comment made so far in the literature about the stereochemistry of organo/halogen exchange at sp^3 C-atoms is that PhSe/Br exchange largely proceeds with inversion[48]. In the diphenylarsino/halogen exchange studied by us there is little prospect of an optically active arsane being converted into an optically active halide, since secondary or tertiary halides rapidly racemize at 110—130 °C[49].

Organo-transition metal groups can be cleaved just as readily as Ph_2Bi from alkyl moieties by halogens (examples: Scheme 28). The possibilities of using such groups as halogen equivalents are however very limited, since all attempts to synthesize reactive carbanions containing organo-transition metal groups have so far failed. Thus, the synthesis of **21** could not be achieved[24j].

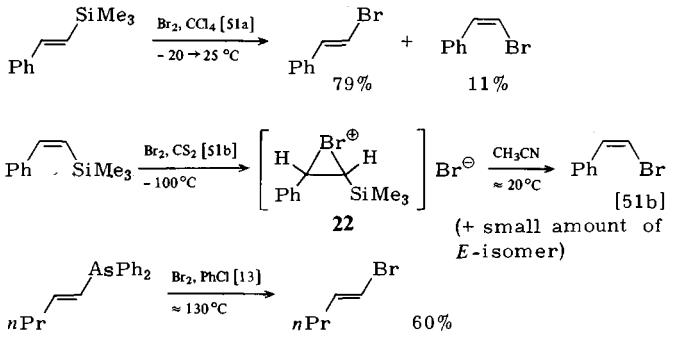


Scheme 28.

3.2.2. *Vinyl-Bound Organoelement Groups*

Groups such as Me_3Si, $(nBu)_3Sn$ (central atom without free electron pair, alkyl ligands), which are attached to an alkyl moiety are unsuitable as halogen equivalents. On the other hand, when bound to a vinyl group or a nucleophilic arene they are very useful: In the case of 1-alkenylsilanes, Me_3Si/Br exchange already takes place specifically at room temperature with rupture of the sp^2 C—Si bond and with retention, whereupon intermediary bromonium ions, *e.g.* **22**, are formed (Scheme 29)[51]. Stannyl groups are exchanged for bromine even more readily than are silyl groups (Scheme 40)[13, 52].

We have found that PhSe and Ph_2As groups attached to vinyl are exchanged for Br in high yields without the double bond being attacked. In contrast to Ph_2As/Br exchange (Schemes 29, 41, 42)[13, 23b], PhSe/Br exchange (Scheme 38) already takes place at 20 °C[4, 47b].



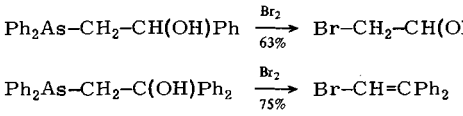
Scheme 29.

3.3. Nucleophilic Reagents with Halogen-Equivalent Groups

3.3.1. Indirect Nucleophilic Halomethylation

Diphenylarsinomethyllithium **4d**: Nucleophilic halomethylations of alkyl halides previously required the four-step process Alk—Hal → Alk—CN → $AlkCO_2H$ → Alk—CH_2OH → Alk—CH_2Hal. With organoelement groups as halogen equivalents the process nowadays involves rather Alk—Hal → Alk—CH_2G → Alk—CH_2—Hal. Besides the well-known reagents $PhSCH_2Li$ and $PhSCH_2Cu$ (Scheme 24) and **4g**, whose disadvantages have been mentioned in Section 3.1, the As-reagent **4d** is particular suitable for this purpose. The Bi-analogue **4f** is less suitable, since on reaction with electrophiles it yields difficultly separable mixtures (so far a pure product has been obtained only from benzophenone), while on using the analogous Sb reagent **4e** (or the analogous Cu(I) compound) organoelement/halogen exchange is relatively unfavorable (see Table 4).

Since reaction of **4d** with aldehydes and ketones or oxiranes yields β- or γ-hydroxyalkylarsanes (yields: 53—94%), it should be pointed out that a γ-hydroxy group causes little interference in diphenylarsino/bromine exchange, whereas a β-hydroxy group may markedly reduce the yield of halide, or, in certain cases, lead to cleavage of water (Scheme 30). In cases where cleavage of water interferes with halogenolysis, it can be profitable to esterify the hydroxy group with acetyl chloride beforehand[24g].

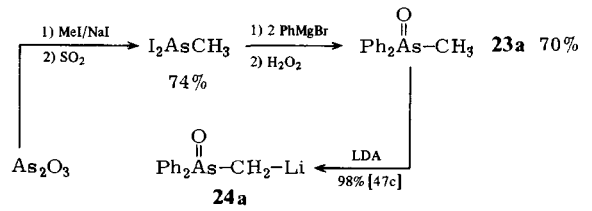


Scheme 30 [44, 45, 47a].

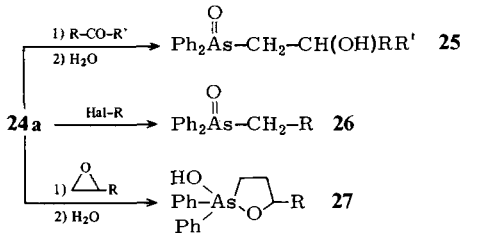
For reactions with aldehydes, ketones, and oxiranes, **4d** can be prepared by iodine/Li exchange (Table 2). For reactions with alkyl halides, on the other hand, the uneconomical synthesis (larger excess of *n*BuLi necessary) by organoelement/Li exchange according to Scheme 9, which leads to reactive **4d** (Table 1), is necessary.

Diphenylarsinoylmethyllithium **24a**: An alternative to **4d** is the more reactive and somewhat more conveniently accessible arsane oxide derivative **24a**[44,45,47c] (Scheme 31: avoidance of the volatile poisonous intermediate Ph_2AsCl and the low temperature synthesis formulated in Scheme 11), which reacts with electrophiles according to Scheme 32.

The main advantage of **24a** is its strongly acidifying diphenylarsinoyl group, which enables coupling of a total of three residues in the α-position (see Section 3.3.2). The disadvantage that a $LiAlH_4$-reduction is necessary after the



Scheme 31.



Scheme 32.

Table 5. Reaction of **24a** with electrophiles in THF at −40→+20°C in the molar ratio 1:1 according to Scheme 32.

Electrophile		Product R	R'	Yield [%]
Butyraldehyde	**25a**	H	*n*Pr	60 [47a]
Benzaldehyde	**25b**	H	Ph	82 [47a]
Cyclohexanone	**25c**	—$(CH_2)_6$—		53 [47a]
Benzophenone	**25d**	Ph	Ph	81 [47a]
Ethyl bromide	**26a**	Et		56 [24h]
n-Propyl bromide	**26b**	*n*Pr		69 [24h]
n-Butyl bromide	**26c**	*n*Bu		72 [47a]
Allyl bromide	**26d**	CH_2—CH=CH_2		70 [47a]
Benzyl bromide	**26e**	CH_2—Ph		72 [24h]
Oxirane	**27a**	H		74 [24g]
Methyloxirane	**27b**	Me		68 [24g]
Ethyloxirane	**27c**	Et		70 [24g]

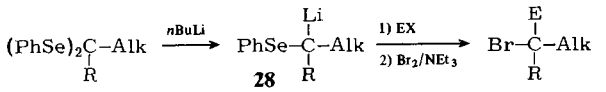
CC-coupling, is not so serious, since the reduction proceeds quantitatively and can be combined with the CC-coupling in a one-pot process.

In reactions with carbonyl compounds and oxiranes the arsinoyl reagent **24a** does not lead to better yields (Table 5) than the arsino reagent **4d**. On the other hand, the yields in reactions with alkyl halides are essentially better (Table 5) than when using **4d** (Table 3), in that the more convenient route *via* Ph_2As—CH_2—I **7d** was chosen for the preparation of **4d**.

Reaction of **24a** with oxiranes and then with water does not lead to γ-hydroxyalkylarsane oxides but to 2-hydroxy-1,2λ⁵-oxarsolanes **27**[24g], which, however, are smoothly reduced by $LiAlH_4$ to γ-hydroxyalkylarsanes, *i.e.* the readily accessible compounds of halogenolysis (cf. Scheme 36).

3.3.2. Indirect Nucleophilic α-Haloalkylation

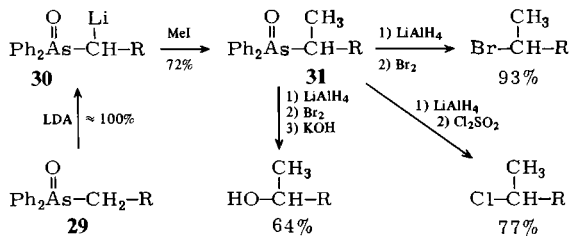
For the introduction of α-bromoalkyl groups into electrophiles (Scheme 33) *Krief et al.*[40,53] used the reagents **28**, which are obtainable by PhSe/Li exchange (cf. *e.g.* Scheme 18).



Scheme 33. EX = electrophile.

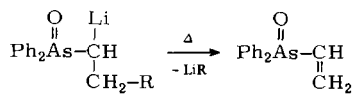
In our method (example: Scheme 34), on the other hand, *α-lithioalkylarsane oxides, e.g.* **30**, are used, which are also readily accessible by H_2O_2-oxidation and lithiation after reaction of PhAsCl with carbanions or of Ph_2AsLi with alkyl halides. The halogenolysis can be combined with a nucleophilic substitution in a one-pot process, whereupon hydroxy compounds or thioethers are immediately formed[24h,54]. The α-lithioalkylarsane oxides thus offer a variety of possibilities for the synthesis of functionalized hydrocarbons.—Also secondary alkylarsane oxides, *e.g.* **31**, can be lithiated with LDA; further reaction with electrophiles, however, is more difficult than with compounds of type **30**.

Owing to their high thermostability (in contrast to corresponding selenium oxides, which already decompose below 20 °C[55]) and tendency to crystallize, the alkylarsane oxides, *e.g.* **29**, necessary as precursors or intermediates



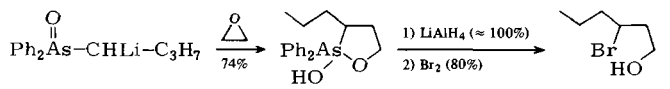
Scheme 34 [24h, 54]; R = C_2H_5.

can easily be isolated. Also their α-lithiation products are usually so thermally stable that they can be heated during reaction with electrophiles. Exceptions are the compounds listed in Scheme 35, and similar compounds: They fragment by LiR elimination[24h,56].



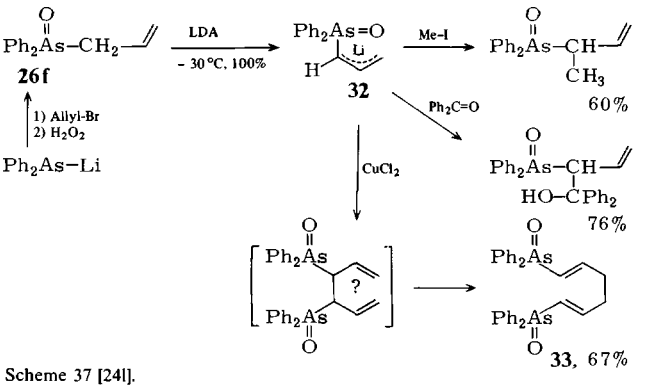
Scheme 35 [24h, 56]. Fragmentation of the educts with R = Ph, Ph_2As, $Ph_2As(O)$ at > −55, <20, and <20 °C, respectively.

Like **24a**, α-lithioalkylarsane oxides also react with oxiranes to give 2-hydroxy-1,2λ^5-oxarsolanes, which can be readily decomposed to open-chain bromides[24g] (Scheme 36).



Scheme 36 [24g].

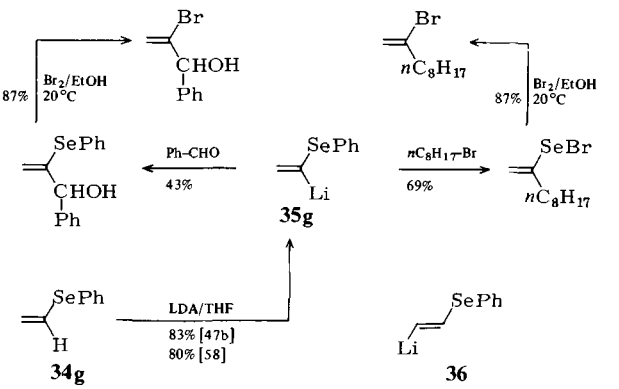
Of the *specific* α-lithioalkylphenylarsane oxides prepared[4], the allyl compounds **32** deserve special mention. Since they react with electrophiles—in analogy to allyllithium compounds with sulfinyl, sulfonyl or phosphonate groups[57]—exclusively in the α-position (Scheme 37), and the CC double bond remains intact during diphenylarsino/bromine exchange at allyldiphenylarsane **20** (Scheme 27), **32** is in all probability suitable for the indirect nucleophilic introduction of α-haloallyl groups into electrophiles. Also worthy of mention is the oxidative coupling of **32** in good yields to give **33**, a diene containing two halogen-equivalent substituents. In the synthesis of **26f** according to Scheme 37 it is advisable to oxidize the very unstable allyldiphenylarsane **20** with 30% H_2O_2 immediately after its formation[24l].



Scheme 37 [24l].

3.3.3. *Indirect Nucleophilic α- and β-Halovinylation*

The thermal instability of **17c** and **17d**[38] (Scheme 23) considerably lowers the value of these reagents for syntheses. A substitute for **17c** is 1-phenylselenovinyllithium **35g**: According to independent observations by *Krief et al.*[58] and by us[4,47b] the electron-withdrawing phenylseleno group of **34g** enables H/Li exchange, to give the sufficiently thermostable and nucleophilic reagent **35g**. Moreover, according to our findings[4,47b] on the products obtained by reaction of **35g** with electrophiles (examples: Scheme 38), phenylseleno/Br exchange in ether or chlorobenzene proceeds quite smoothly already at room temperature, even if a hydroxy group is in the β-position to the phenylseleno group. **35g** is therefore a suitable reagent for *indirect nucleophilic α-halovinylation.*

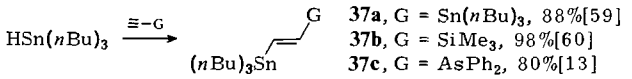


Scheme 38 [4, 47b].

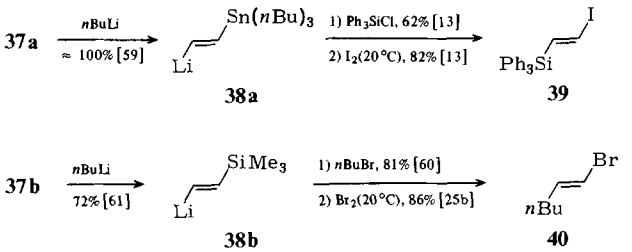
When using **35g**, account should be taken of its tendency to undergo elimination of PhSeLi—particularly in

the presence of hexamethylphosphoric triamide (HMPA)[58]. A small HMPA content is, however, advantageous for reaction with alkyl halides[58].—The tellurium analogue **35h** (see Section 4.1.3) is no alternative on account of its poorer accessibility and lower nucleophilicity.

The thermolability is greater when halogen and lithium, as in **17a** and **17b**, are attached *vicinal* to a CC double bond than when attached at the *geminal* position (Scheme 23). Whereas a substitute organoelement reagent for *cis*-compounds of the type **17b** is to our knowledge unknown, there are equivalents for the *trans*-compound **17a**: Unlike the extremely unstable Se-compound **36**[25a], the Li-compounds **38a** and **38b** synthesized for another purpose by *Corey et al.*[59] and *Cunico et al.*[60], respectively, are suitable in this respect, as is demonstrated by synthesis of the halides **39** and **40** (Schemes 39 and 40). The Sn-reagent **38a** is, of course, hardly recommendable, since it is extremely difficult to separate the desired product from the tetrabutyltin and other products that are always formed.

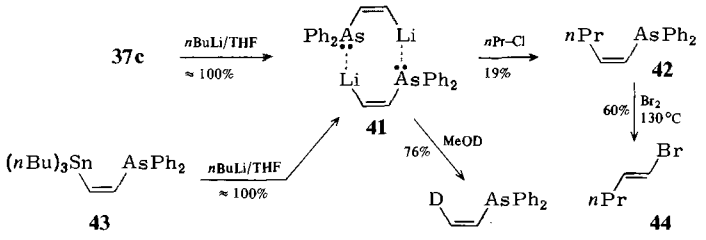


Scheme 39.



Scheme 40.

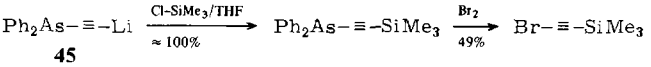
In the case of the As-reagent **41** synthesized by us, the *Z*-configuration is presumably stabilized by the complexation formulated in Scheme 41. Unfortunately, the Ph_2As/Br exchange requires such severe conditions that inversion of configuration occurs[62].—The educts for **41** are accessible by hydrostannation according to Scheme 39, where up to ≈10% of the *Z*-isomer **43** is formed as well as **37c**.



Scheme 41 [13].

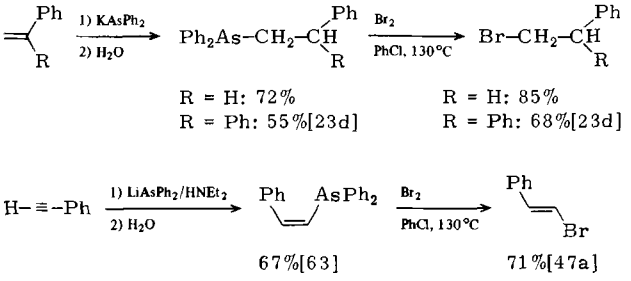
3.3.4. *Indirect Nucleophilic Haloethynylation*

Such conversions have rarely been investigated. An As-reagent, namely **45**, is also suitable for this purpose; it is conveniently accessible by H/Li or Ph_2As/Li exchange (Scheme 6). That the diphenylarsino- and not the trimethylsilyl-group of the intermediate is exchanged for bromine is surprising.



3.3.5. *Strongly Nucleophilic Equivalents for Hal⊖*

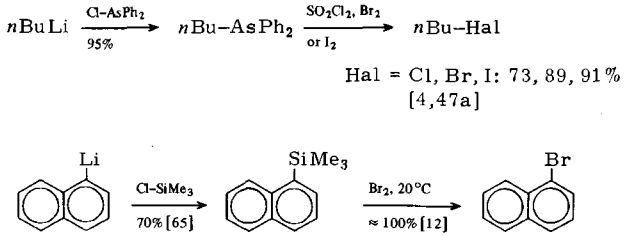
When halide ions with extremely high nucleophilicity are desirable in synthetic operations, reaction with $Ph_2As^{\ominus}$ (Ph_2As—Cl or Ph_2As—$AsPh_2$ + Li, Na, K) or $PhSe^{\ominus}$ (PhSe—SePh + $NaBH_4$) with subsequent organoelement/halogen exchange is recommended. Here, the diphenylarsenide ion generally has the higher nucleophilicity. If in such a reaction the organoelement group is coupled with a *primary* C-atom, $Ph_2As^{\ominus}$ might, as a rule, also be more suitable than $PhSe^{\ominus}$, since the yield on organoelement/halogen exchange is better (see Table 4). Scheme 42 shows some applications.



Scheme 42.

3.4. Electrophilic Reagents with Halogen-Equivalent Groups

In attempts to halogenate carbanions with halogens, CC-linkage by oxidative coupling is not rarely the main reaction. As a rule, better results are obtained with CCl_4 or CBr_4[64]. If the Li atom attaches to an sp^3 C-atom a favorable alternative is arsanation with chloro(diphenyl)arsane followed by diphenylarsino/halogen exchange. In the case of alkenyl- and aryllithium compounds, silylation with trimethylchlorosilane followed by trimethylsilyl/halogen exchange is more favorable (examples: Scheme 43).



Scheme 43.

Organoelement equivalents for vinyl halides are mentioned in Section 4.2.1.

4. Electron-Withdrawing Effect of Organoelement Groups and Synthetic Uses

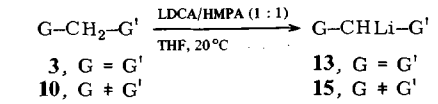
4.1. Acidification by Heavy Main-Group Elements

4.1.1. H/Li-Exchange at G_2CH_2

According to the findings in Section 2.2.1, Ph_nEl-groups with E = Sn, Pb, As, Sb, Bi stabilize a lithiated C-atom directly attached to them. Moreover, the reactions with the tri*alkyl*stannyl compounds **4i** and **4j** (Table 2) showed, in the case of tin, that phenyl ligands are not decisive for this stabilization. The question now arose, whether heavy main-group elements in general could detectably acidify an attaching CH-group.

We initially investigated the effect of bases on bis(triphenylstannyl)methane **3b**, whose tendency to undergo stannyl/Li exchange precluded the use of organolithium compounds as base. After a number of fruitless attempts[66a], lithiation was finally accomplished with the aid of the bulky lithium dicyclohexylamide (LDCA) in presence of up to 92% HMPA[23e]. Analogous compounds were also lithiated under the same conditions, at room temperature according to Scheme 44[67] (Table 6); in the case of the Bi-compound **3f**, decomposition reactions prevent detection of lithiation.

That the acidifying action of heavy main-group elements has only just been discovered might be due to the high electrophilicity of the corresponding organoelement groups. This promotes direct attack at these groups by bases such as *n*BuLi or PhLi, which effect organoelement/Li exchange (cf. Scheme 51).



Scheme 44.

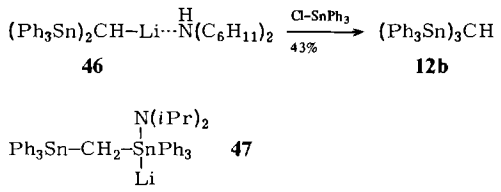
Table 6. Lithiation of **3** and **10** to **13** and **15**, respectively, according to Scheme 44 [67].

	G	Yield [%]		G	Yield [%]
13l	Ph_3Si	0 [24n]			
13a	Ph_3Ge	0 [23f]	**13d**	Ph_2As	63 [24e]
13b	Ph_3Sn	92 [23e]	**13e**	Ph_2Sb	68 [24h]
13c	Ph_3Pb	67 [25a]	**13f**	Ph_2Bi	decomp. [24n]
15c	Ph_3Sn—CHLi—$AsPh_2$, yield 67% [24b]				
15d	Ph_3Pb—CHLi—$AsPh_2$, yield 32% [24b]				

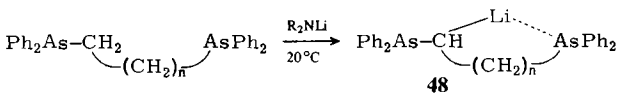
The Li-compounds **13** obtained by H/Li exchange disappointingly showed little reactivity towards carbonyl compounds and other electrophiles: For example, the most investigated of such compounds, namely bis(triphenylstannyl)methyllithium **13b**, reacted in preparatively useful yields, if D_2O or H_2O is ignored, only with Ph_3SnCl, whereby tris(triphenylstannyl)methane **12b**[23e,67] was obtained for the first time[37].

If, on the other hand, **13b** is synthesized by organoelement/Li instead of H/Li exchange, it is very reactive (see Section 2.3.2). As experiments with **13b** in the presence of dicyclohexylamine or HMPA have shown, deactivation is effected by the amine and not by HMPA[23e]. Probably the 1 : 1 complex **46** is formed, whose nucleophilic center is strongly shielded by bulky residues.

Since LDA has a greater tendency to undergo nucleophilic addition than the bulky LDCA, it was surprising that **3b** could be recovered largely unchanged after reaction with LDA (practically no lithiation). Presumably the ate-complex **47** is formed, which decomposes on addition of water, with generation of **3b**.



In compounds **3**, *two* organoelement groups acidify the methylene group. It could be shown with the aid of the reactions outlined in Scheme 45, that even *one* diphenylarsino group makes the α-methylene group capable of lithiation if a second group of the same kind supports it by chelation[23c].

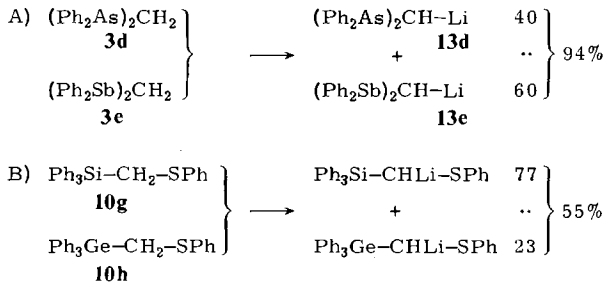


Scheme 45 [23c, 24b, 24c].

Conditions	**48**, n =	Yield/[%] 1	2	3	4	5	6
LDA/THF		0	36	36	32	21	0
LDCA/HMPT		63	49	60	54		

4.1.2. Influence of Element and Ligand on the Acidification

We have compared the acidifying effect of heavy and of light main-group elements by H/Li exchange on the compounds **3** under competing conditions, the experimental conditions having to be varied for practical reasons[66b]. Scheme 46 A shows a typical competition experiment. The results are collected in Scheme 47.

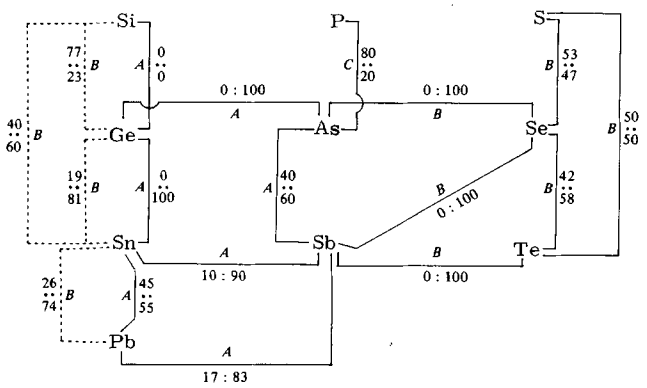


Scheme 46. Conditions: A) LDCA/HMPA (1 : 1), THF, 20 °C, 0.5 h; B) LDA/THF, −50 → −10 °C, 2.5 h.

Since a comparison of the groups Ph_3El in which El = Si, Ge, Sn, Pb was either impossible, or possible to only a lim-

ited extent, owing to the very low acidity of compounds **3**, El = Si and Ge [**3a**], these groups were combined with the distinctly acidifying phenylthio group to give, *e.g.*, compounds **10g** and **10h**, respectively. The results of competition experiments with these compounds[24j] (example: Scheme 46 B) are given alongside the dotted brackets in Scheme 47. The degrees of lithiation were determined by deuterolysis with D_2O and ^{1}H-NMR analysis of the products.

From the molar ratios of the lithiation products it is concluded that the elements of the 4th row (Sn, Sb, Te) are more strongly acidifying than the homologous elements of the 3rd row (Ge, As, Se), and equally as strongly acidifying as the homologous elements of the 2nd row. Furthermore, a marked increase in acidifying action was observed on going from the 4th row element Sn to the 5th row element Pb, and—as expected—on going from the 4th→5th→6th group.—Since the molar ratios of the lithiation products did not change in experiments carried out over prolonged periods, thermodynamic acidity must be involved.



Scheme 47. For explanation see text. Lithiation conditions: *A* as in Scheme 46 A [24j, 24n]; *B* as in Scheme 46 B [24a, 24j]; *C* *n*BuLi + 2 TMEDA, THF, 20 °C, 0.5 h [24g].

Since bis(tri*methyl*silyl)methane **3k** is lithiated largely at the methylene group by *n*BuLi + HMPA[68a], whereas all attempts at lithiation on the analogous hexaphenyl compound **31**[24n] failed, it would appear that phenyl ligands in comparison to methyl ligands reduce the acidifying effect of the element[4]. Individual and competition experiments, mainly performed on compounds **10**, in which the group under examination is combined with a phenylthio- or phenylseleno-group, later showed a reverse pattern in the ratios (examples: Table 7).

3k $(Me_3Si)_2CH_2$ **3l** $(Ph_3Si)_2CH_2$

Table 7. Competing lithiation of G—CH_2—G' **10** for determining the influence of ligands on the acidifying action of main group elements.

Substrates		Yield G—CHLi—G' rel.	abs. [%]
Me_3Si—CH_2—SPh/Ph_3Si—CH_2—SPh	[a]	6 : 94	80 [47a]
Me_3Si—CH_2—SePh/Ph_3Si—CH_2—SePh	[b]	23 : 77	53 [24j]
Me_3Ge—CH_2—SPh/Ph_3Ge—CH_2—SPh	[a]	12 : 88	≈ 100 [24j]
Me_3Ge—CH_2—SePh/Ph_3Ge—CH_2—SePh	[b]	0 : 100	56 [24j]

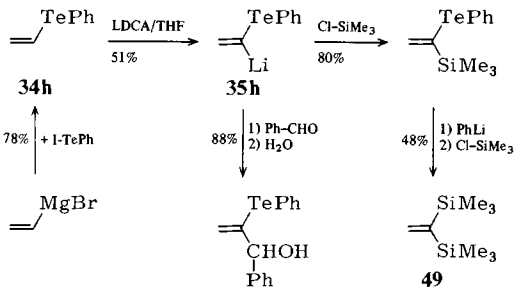
[a] LDA, THF, −50→−10 °C, 2.5 h; [b] LDCA/HMPA (1 : 1), ether/THF (3.5 : 1), 20 °C, 2 h.

Accordingly, the failure of attempted lithiation of **31** can only be explained thus: Owing to the small C—Si bond length of ≈ 1.93 Å (corresponding bond lengths in the case of Ge, Sn, Pb: ≈ 1.98, 2.18, ≈ 2.29 Å)[69] the methylene group of **31** is so strongly shielded that, other than in the case of the corresponding Sn- or Pb-compound (see Section 4.1.1) or **3k**, it cannot be attacked by lithiating reagents.

4.1.3. H/Li Exchange at Phenyltelluroethene

Since the PhTe group is superior rather than inferior to the PhSe group in the acidifying action[24a] (Scheme 47), and since phenylselenoethene **34g** is amenable to H/Li exchange (see Section 3.3.3), it was of interest to us whether this also holds for phenyltelluroethene **34h**. The question at hand was also whether organoelement/Li exchange can be suppressed in favor of H/Li exchange.

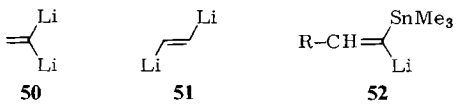
Whereas reaction of *n*BuLi with the recently prepared compound **34h**[24a] (Scheme 48) leads to formation of only ≈ 10% α-lithio(phenyltelluro)ethene—as expected the main reaction is organoelement/Li exchange—the yield increases to ≈ 50% on using the bulky bases lithium dicyclohexylamide (LDCA) or lithium-2,2,6,6-tetramethylpiperidide in THF at −70 °C. A further increase in yield was not possible[24a].



Scheme 48 [24a, 47a].

In view of the very good yields obtained for organotelluro-compounds on reaction of **35h** with benzaldehyde or trimethylchlorosilane (Scheme 48), the failure of the reaction with allyl bromide or 1-iodopropane was surprising.

The products to be expected, and actually synthesized from **35h** and electrophiles, contain the phenyltelluro group, which is readily exchangeable for Li; hence, the vinyl group can be coupled with a second electrophile to give, *e.g.*, **49**[68b]. **35h** may therefore be regarded as equivalent for 1,1-dilithioethene **50**, similarly to **38a**[59] (Scheme 40) as equivalent for *E*-1,2-dilithioethene **51**.—



50 **51** **52**

Equivalent reagents for 2-substituted 1,1-dilithioethenes are the recently described compounds **52**, which are accessible by stannyl/Li exchange[70].

4.1.4. What Causes the Stabilization of Carbanions by Heavy Main-Group Elements?

This stabilization of carbanions is proven by the exchange reactions (organoelement/Li, halogen/Li, H/Li exchange) outlined. The question as to the cause, however, cannot as yet be answered unequivocally: According to *ab initio* calculations on REl—$CH_2^{\ominus}$ anions (El = S, Se) the stabilization of carbanions by thio- or seleno-groups is due to the polarizability of S and Se, and to a stereoelectronic effect[71]. If polarizability does in fact play an essential role, then stabilization by the "soft" elements of the 4th and 5th row is readily understandable.

The relatively high acidity of C—H bonds alpha to 2nd-row elements Si, P, S is still usually explained, even today, in terms of a (p→d)π orbital overlapping in the respective anions. A corresponding overlapping is unlikely in the case of a 4th- or 5th-row element, owing to the distinctly longer C—El bond. That long pd hybrid orbitals of 4th- and 5th-row elements participate, as has been discussed for explanation of the strong ring current effect of arsa- and stiba-benzene[72], is, however, also worth considering here. It might also be possible that alkyllithium compounds containing a heavy main-group element in the α-position form particularly stable aggregates and are thus thermodynamically favorable. Here, the formation of ate-complexes, *e.g.* **53**, is the first likelihood, provided that the heteroatom has no free electron pair.

$$\underset{\textbf{4c}}{2\ Ph_3Pb{-}CH_2{-}Li} \longrightarrow \underset{\textbf{53}}{Ph_3Pb{-}\overset{\overset{Li}{|}}{C}H_2{-}Pb(Ph)_3{-}CH_2{-}Li}$$

4.2. Nucleophilic Addition and Cycloaddition to Organoelement-Substituted Ethenes

4.2.1. Chain Expansion of Carbanions

It was known from the literature that R_nEl-substituted ethenes **34**, El = SiP, S, Ge, add to the double bond of alkyllithium compounds[73] because of the electron-withdrawing action of these elements. Since As and Se are likewise electron-withdrawing (cf. Section 4.1.2), and since alkyl-bound Ph_2As- and PhSe-groups are favorable halogen equivalents (Section 3.2.1), we checked whether the chain-lengthening of carbanions with diphenylarsino- **34d** and phenylseleno-ethene **34g** formulated in Scheme 49 could be realized, and found our expectations confirmed.

$$\underset{\textbf{34}}{Alk{-}Li + \overset{G}{=\!\!\diagup}} \longrightarrow \underset{\textbf{54}}{Alk{-}\overset{\overset{Li}{|}}{C}H_2{-}CH{-}G} \xrightarrow{H_2O} \underset{\textbf{55}}{Alk{-}(CH_2)_2{-}G} \xrightarrow{Br_2} \underset{\textbf{56}}{Alk{-}(CH_2)_2{-}Br}$$

d, G = Ph_2As
g, G = PhSe

Scheme 49. Yields: Table 8.

Table 8. Synthesis of **55** and **56** from **34** and alkyllithium compounds (molar ratio 1 : 1) according to Scheme 49. Yields based on Alk—Li.

Alk	G	Yield [%] 55	56	G	Yield [%] 55	56
C_2H_5	Ph_2As	37 [a]		PhSe		
n-C_4H_9	[24o]	95 [a]	82	[23a]	72 [b]	32
s-C_4H_9		71 [b]	84		25 [b]	28
t-C_4H_9		57 [b]			25 [b]	

[a] Reaction in THF; [b] reaction in ether [46].

In each case, diphenylarsinoethene **34d** gave far better yields than phenylselenoethene **34g** (Table 8) in the addition and the halogenolysis (see Section 3.2.1). The drawback of using **34g** as substrate for the addition may be due to the fact that α-lithiation to **35g** (see Section 3.3.3) and phenyl/alkyl exchange to give alkylselenoethene compete with the addition[58].—The reactions formulated in Scheme 49 reveal **34d** as equivalent for vinyl halides, which cannot add carbanionic compounds because of polymerization.

α-Lithiated alkyldiphenylarsanes **54d** have been made accessible for the first time *via* the reaction of **34d** formulated in Scheme 49. With these, as with diphenylarsinomethyllithium **4d** (see Section 3.3.1), α-arsino-, and thus α-haloalkyl-groups (see Section 3.3.2) can be incorporated into electrophiles (example: Scheme 50).—Electrophiles have also been reacted with Se derivatives **54g**[58].

$$\underset{\textbf{54d}}{Alk{-}\overset{\overset{Li}{|}}{C}H{-}AsPh_2} \xrightarrow[2)\ H_2O]{1)\ Ph\text{-}CHO(THF)} \underset{68\%}{Alk{-}\overset{\overset{HO{-}CH{-}Ph}{|}}{C}H{-}AsPh_2}$$

Scheme 50 [24o]. Alk = *n*-C_5H_{11}.

According to our observations, R_nEl-substituted ethenes **34** do not react with 4th- and 5th-row elements according to Scheme 49, most likely due to organoelement/Li exchange. Thus, there is a clear line of demarcation between suitable elements (area circled in Scheme 51) and unsuitable elements for such reactions. The same applies for cycloadditions (Section 4.2.2).

Si	P	S
Ge	As	Se
Sn	Sb	Te
Pb	Bi	

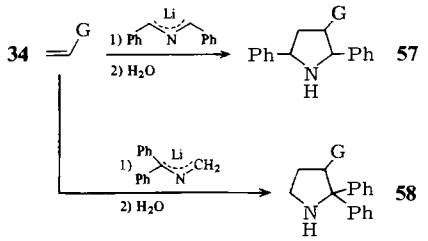
Scheme 51. The group of elements circled can react according to Scheme 49.

4.2.2. Organoelement Groups as Removable Auxiliary Groups in 1,3-Anionic Cycloadditions

The scope of the "1,3-anionic cycloaddition" type of reaction[5] is considerably limited by the fact that, for stabilization of the heteroallyl anions and activation of the substrates, aromatic moieties are required which can be removed after reaction.—This problem was remedied by the observation that organoelement groups like PhS, PhSe, Ph_2P and Ph_2As, which are readily removable after the cycloaddition, so activate olefinic double bonds that cycloaddition of 2-azaallyllithium compounds according to Scheme 52 is possible[74] (yields: Table 9). The cleavage of these auxiliary groups can be accomplished by hydrogen-

ation with Raney-nickel (PhS, PhSe, Ph_2As) or by bromolysis (Ph_2As, PhSe) (examples: Scheme 53). The Ph_2P group may be removable after oxidation by Horner reaction.

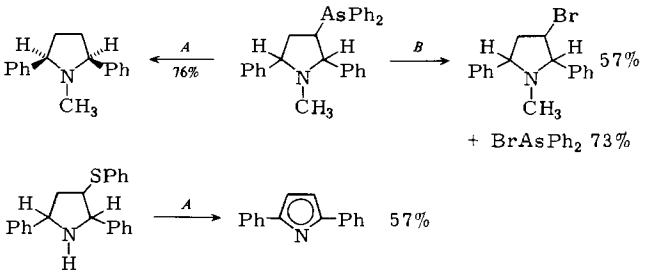
Me_3Si, Ph_3Si[75] and Ph_3Ge groups are likewise activating (Table 9), but they are difficultly removable, while corresponding groups containing the 4th- and 5th-row elements Sn, Sb, Te, Pb, Bi are unsuitable because of organoelement/Li exchange (see Scheme 51).



Scheme 52. G and yields: Table 9.

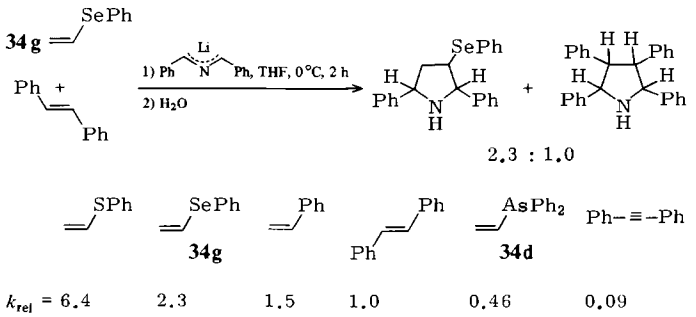
Table 9. Synthesis of **57** and **58** from **34** and 1,3- and 1,1-diphenyl-2-azaallyllithium, respectively, in THF according to Scheme 52 [74].

	G	Yield [%]		
		57		**58**
a	Ph_3Si	86 [75]	43 [25a]	31 [25a]
	Me_3Si	57 [75]		—
	Ph_3Ge	29 [25b]		31 [25b]
d	Ph_2P	>42 [23i]		>65 [23i]
	Ph_2As	65 [24o]		0 [24o]
g	PhS	68 [25a]		64 [25a]
	PhSe	77 [23a]		42 [23a]



Scheme 53 [24o]. *A:* Raney-nickel/EtOH, 20°C; *B:* 1) Br_2/CCl_4 0°C, 2) 120°C.

In competition experiments, in which two olefins were allowed to react with 1,3-diphenyl-2-azaallyllithium in the molar ratio 1:1:1, we determined the relative rate constants quoted in Scheme 54. The gradation in readiness to



Scheme 54.

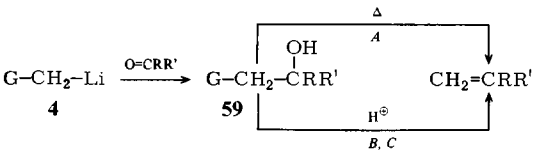
undergo cycloaddition along the series PhS> PhSe> Ph_2As directly corresponds to the relative acidifying effect of these groups revealed in Scheme 47. Thus, as expected, the tendency to undergo cycloaddition depends on the degree of stabilization of a negative partial charge in the α-position to the organoelement group. The comparison phenylthioethene : phenylethene (styrene)—about four times more rapid reaction and easily removable activating groups of the sulfur compound—clearly demonstrates the improvement achieved.

5. Organo Heavy-Metal Groups as Leaving Groups in β-Eliminations

5.1. Novel Reagents for Carbonyl Olefination

5.1.1. Synthesis of Terminal Olefins

The reagents **4** listed in Table 10 (synthesis: Sections 2.2.1 and 2.2.3) react with aldehydes and ketones to give β-hydroxy compounds of the type **59**[2,4,26,31].



Scheme 55. Methods *A, B, C* see text.

Table 10. Synthesis of **59** from 4 and carbonyl compounds (molar ratio 1:1) according to Scheme 55. Yield of isolated product.

G	Yield [%] on reaction with				
	PhCHO	Ph_2CO	*n*PrCHO	$C_6H_{10}O$ [c]	MeCOPh
Ph_3Ge [23f]	74 [a] 58 [b]				65 [a]
Ph_3Sn [b] [24k]	65	0	59	37	41
Ph_3Pb [b] [24k]	71	54		46	9
Ph_2As [25a, 24i]	69 [a] 92 [b]	94 [b]	62 [a] 75 [b]	70 [a] 73 [b]	
Ph_2Sb [a] [25b]	39	45		61	
Ph_2Bi [a] [24n]		48			

[a] Prepared by organoelement/Li exchange. [b] Prepared by halogen/Li exchange. [c] Cyclohexanone.

Table 11. Carbonyl olefinations according to Scheme 55, for example, of benzaldehyde. Method *A:* dry heating to 180°C, *B:* $HClO_4/CH_3OH$, 20°C; *C:* SiO_2/THF, 20°C.

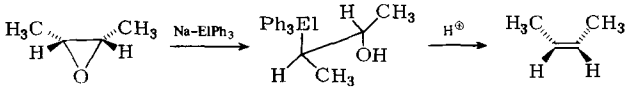
G	Styrene yield [%]		
	A	*B*	*C*
Ph_3Ge [23f, 24j]	0 [a]	95 [a], 94 [b]	0 [a]
Ph_3Sn [24k] [c]	84 [a], 87 [b]	68 [a], 80 [b]	56 [a]
Ph_3Pb [24k]	62 [a], 64 [b]	77 [a], 67 [b]	69 [a]
Ph_2As [25a]	35 [a]	15 [a]	0 [a]
Ph_2Sb [25b]	48 [a]	71 [a], 61 [b]	45 [a]

[a] Yield based on **59**. [b] Yield based on **4**, since **59** not isolated. [c] Method *A:* Heating to 110°C.

With exception of the Ge-derivatives and the Bi-compound obtained by reaction with benzophenone, the products **59** undergo β-elimination on heating to give terminal olefins (Scheme 55, Method *A*)[4,26,76]. The decomposition temperature in the case of the Sn-compounds (100—120°C) is lower than in the case of the Pb-, Sb-, and As-

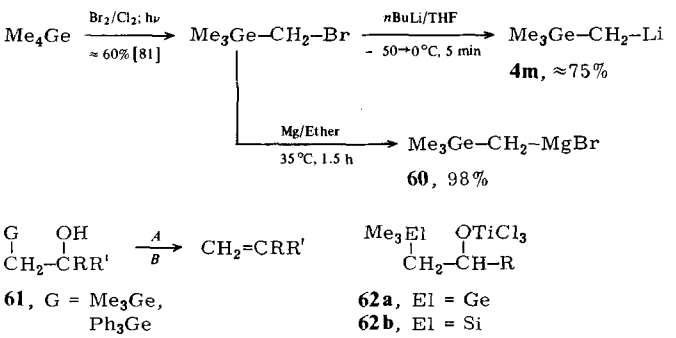
compounds (160—180 °C). Accordingly, the yield of olefin is usually somewhat better in the former case; the As-compounds give the lowest yields of olefin. Apart from by heating (in toluene at 110 °C, in chlorobenzene at 130 °C, or without solvent at 180 °C; Method *A*) the formation of olefin can also be achieved by reaction with $HClO_4$ (Method *B*)[76]. A much simpler and more gentle method is to pass the THF-solution of **59** through a short silica-gel column (Method *C*)[76,77]. Method *C* fails in the case of Ge- and As-compounds and is thus apparently limited to compounds **59** containing organoelement groups of 4th- and 5th-row elements. Table 11 shows the yields obtained in carbonyl olefinations for the example of benzaldehyde (yields on the use of other carbonyl compounds: [4,26,31,76]). The Bi-compound obtained from benzophenone gave 0, 61, and 91% yields of 1,1-diphenylethene on using Methods *A*, *B*, and *C*, respectively[24m].

Prior to our investigations β-hydroxy compounds of type **59**, G = Ph_3Sn, Ph_3Pb, were synthesized by *Davis* and *Gray*[78] by nucleophilic ring-opening of oxiranes according to Scheme 56, followed by decomposition with acid to the olefin. Since the overall reaction proceeds with retention, and the C—O bond is undoubtedly opened by attack from the rear, the olefin is formed by *anti*-elimination. This is of interest in connection with the findings described in Section 5.1.2.



Scheme 56. El = Sn, Pb [78].

Aside from **4a**, the first Ge-reagent used for carbonyl olefinations[23f,24j,76] (Tables 11 and 12), the analogous anionoid tri*methyl*germyl compounds **4n** and **60** are also suitable for this purpose (Scheme 57)[24j]. They have the advantage over **4a** in that the β-hydroxyalkylgermanes **61** (cf. **59**) obtained by reaction with aldehydes and ketones, like the analogous Si-compounds[79,80], are also decomposed to olefins by KH (presumably *syn*-elimination) as well as by acids (presumably *anti*-elimination), the yields being very good in each case (Table 12). These findings can possibly be exploited for stereospecific carbonyl olefinations (cf. Section 5.1.2). In comparison to the analogous, less-expensive Si-reagents, it would appear to be advantageous in the case of the Ge-reagents **4a**, **4m**, **60**—as well as **63a** and **63b** (Table 13)—that the nucleophilicity is somewhat higher as a result of the particularly low stabilization of carbanions by Ge (see Scheme 47).



Scheme 57 [24j]. *A*, *B* see Table 12.

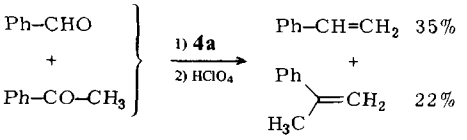
In the synthesis of organic compounds the organoelement functional groups must be removed again. Carbonyl olefination with Ge-reagents (see also Section 5.1.4) thus also deserves attention, since it is the mildest method for the removal of organogermanium groups from C-atoms[82].

Table 12. Carbonyl olefinations according to Scheme 57 with $Me_3Ge—CH_2—Li$ **4m** and $Ph_3Ge—CH_2—Li$ **4a** as well as $Me_3Ge—CH_2—MgBr$ **60** to give terminal olefins. Decomposition of the β-hydroxy compounds **61** obtained by hydrolysis with H_2O; Method *A*: with $HClO_4$ at ≈ 20 °C; *B*: with KH at ≈ 20 °C [24j].

	Carbonyl compound	Olefin yield [%] *A* [b]	*B*
4m [a]	Heptanal	90 (91)	88
	Phenylacetaldehyde	95 (88)	87
	Benzaldehyde	94 (87)	81
	4-(*tert*-Butyl)-cyclohexanone	91 (79)	90
	Acetophenone	91 (63)	95
4a [c]	Heptanal	99	no olefin formation
	Phenylacetaldehyde	96	
	Benzaldehyde	94	
	Acetophenone	96	

[a] Molar ratio **4m** : carbonyl compound = 1.5 : 1. [b] Values in brackets: Yields on analogous reaction with **60**. [c] Molar ratio **4a** : carbonyl compound = 1.3 : 1.

4a, 4n, 60 and the analogous Si-reagents are unsuitable for aldehyde-selective carbonyl olefinations, since they also react rapidly with ketones (example: Scheme 58). On the other hand, we were able to carry out *"highly aldehyde-selective" carbonyl olefinations* for the first time with the transition-metal reagents quoted in Table 13. These were generated *in situ* from **60** and the analogous Si-compounds prepared by reaction with $TiCl_4$ in ether or with $CrCl_3$ in THF (examples: Table 13)[83].



Scheme 58 [24j].

Table 13. Yields [%] of terminal olefins on using aldehyde-selective carbonyl olefinating reagents **63** (molar ratio **63** : carbonyl compound = 3 : 1) [83].

	[a] Heptanal [b] Nonanal [c] Benzaldehyde	[a] 5-Nonanone [b] Acetophenone [c] 4-(*tert*-Butyl)-cyclohexanone
$Me_3Ge—CH_2—TiCl_3$	[a] 88	
63a [24j]	[b] 76	
	[c] 76	[c] 0
$Me_3Ge—CH_2—CrCl_2$	[a] 67	
63b [24j]	[b] 58	[c] 0
$Me_3Si—CH_2—TiCl_3$	[a] 65	[a] 0
63c [47a, 84]	[b] 61	[b] 3
	[c] 59	[c] 8
$Me_3Si—CH_2—CrCl_2$	[a] 47	[a] 0
63d [47a, 84]	[b] 45	[b] 0
		[c] 0

The mechanism of carbonyl olefination with the reagents **63** varies considerably. When Ti-reagents **63a, c** are employed, olefination already occurs before hydrolysis[85], whereas when the Cr-reagents **63b, d** are used it occurs only after the neutral hydrolyzate has been treated with mineral acid. The intermediates **62** obviously decompose rapidly with formation of olefin.

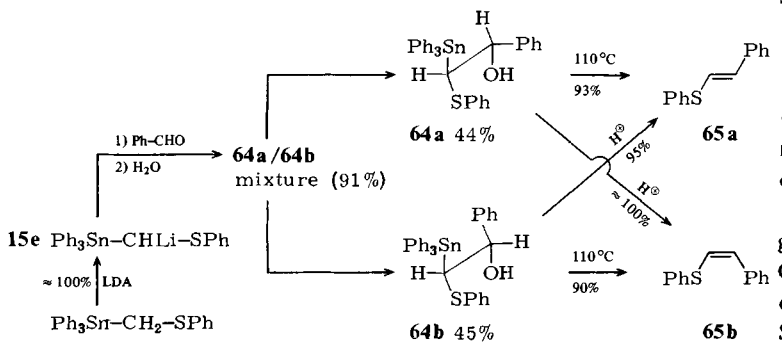
5.1.2. Stereospecific Carbonyl Olefination to the Z- or E-Olefin

In highly stereoselective olefinations a distinction is made between methods "without isolation of intermediates" (*e.g.* influencing the steric course of the Wittig reaction according to *Schlosser* and *Christmann*[86]) and methods "with isolation of intermediates". Of the latter the Peterson carbonyl-olefination[79] is, in principle, especially advantageous: Since the intermediary β-hydroxalkyltrimethylsilanes can be decomposed at choice by *syn-* or by *anti*-elimination (action of KH or acid)[80], an aldehyde or an unsymmetric ketone can be converted selectively and in high yield into an *E-* or *Z*-olefin, provided the *threo-* and *erythro*-form of the β-hydroxyalkylsilane can be separated. In contrast, in the case of other carbonyl olefinations either only *syn-* (Wittig-like reactions) or only *anti*-elimination (use of Se-reagents[87]) is possible.

In principle, however, the scope of the Peterson carbonyl-olefination is considerably limited. In the case of the readily accessible Si-reagents with an electron-withdrawing moiety on the carbanionic center, the alcoholic intermediates are isolable in only very low yields or not at all, owing to the instability of their anion (see Scheme 63).

According to our findings, stereospecific carbonyl olefinations to give either the *E-* or the *Z*-olefin are also possible with stannyl- and plumbyl-stabilized carbanions[4,24k,25a,88]. Since the alcoholic intermediates can almost always be isolated when using these reagents (exception: Scheme 62) it would appear that they have broader scope than those of the trimethylsilyl derivatives (Peterson carbonyl olefination).

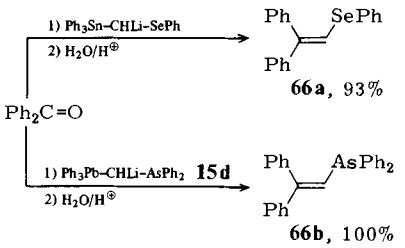
The synthesis of the β-phenylthiostyrenes **65a** and **65b** from benzaldehyde according to Scheme 59[4,88] has been investigated in most detail[4,88]: The action of perchloric acid in methanol on the *threo*-intermediate **64a**, separated quantitatively by HPLC from the isomer **64b**, led exclusively to the *Z*-olefin, while heating gave exclusively the *E*-olefin. The former reaction is, according to *Davis* and *Gray*[78] (see Section 5.1.1), an *anti*-elimination; hence, *syn*-elimination takes place on heating. The *erythro*-isomer **64b** was decomposable in the same way. Accordingly, benzaldehyde can be converted at choice with *phenylthio(triphenylstannyl)methyllithium* **15e** into the *E*-olefin **65a** (83%) or the *Z*-olefin **65b** (84%). Under analogous conditions the Pb-analogue of **15e** gave either pure **65a** or a 1:2 mixture of **65a** and **65b**. Thus, Sn-reagents would seem to be more suitable than the Pb-analogues for stereospecific syntheses of *Z*-olefins from carbonyl compounds.



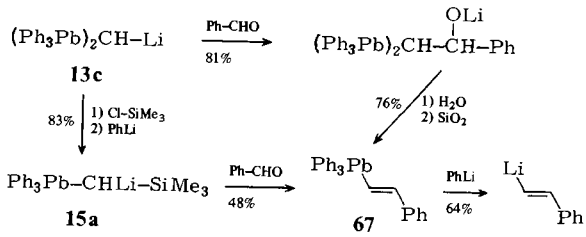
Scheme 59. For simplicity only one enantiomer of each of the alcoholic intermediates **64** is formulated.

5.1.3. Other Syntheses of Organoelement-Substituted Olefins by Carbonyl Olefination

Organoelement-substituted ethenes, *e.g.* of type **34**, have a variety of uses in organic synthesis. Some of the more useful reactions (examples: PhS group: indirect nucleophilic acylation with 1-phenylthiovinyllithium[89]; PhSe, PhTe, Ph_2As groups: Schemes 38, 48, 49, 52) may be extended to correspondingly substituted higher olefins. The synthesis of such compounds—also using the stereospecific method presented in Section 5.1.2—is one convenient use of carbonyl olefination reagents containing stannyl- or plumbyl-leaving groups. Some such syntheses are outlined in Schemes 60 and 61.



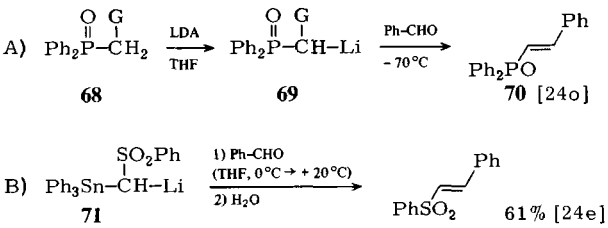
Scheme 60 [24m]. The yields of **66a** and **66b** on elimination by heating are 74 and 75%, respectively.



Scheme 61 [24m].

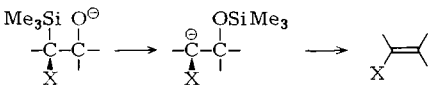
The yields obtained on synthesizing the plumbyl olefin **67** *via* two routes (Scheme 61) show that Ph_3Pb can be more favorable than Me_3Si as leaving group. In each case only the *E*-olefin is formed.

In analogous experiments, the organo heavy-metal groups behaved surprisingly: the Li-compounds **69**, G = Ph_3Sn, Ph_3Pb, Ph_2Sb, PhTe, did not react with benzaldehyde in the sense of a Horner reaction but according to Scheme 62, even at −70°C, with immediate cleavage of the organo heavy-metal group to give β-(diphenylphosphinoyl)styrene **70**[24o,90].



Scheme 62. Yield of **70** from **68**, G = Ph_3Sn, Ph_3Pb, Ph_2Sb, PhTe = 92, 71, 25, 41% [90].

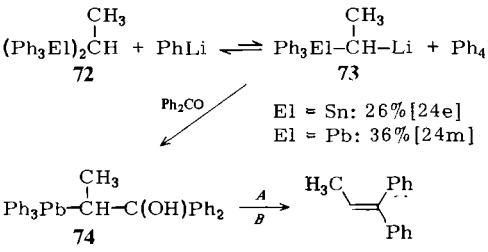
Thus, in this case even the phenyltelluro-group which is otherwise unsuitable for this purpose is relatively suitable as leaving group. The observed promotion of β-elimination by a strong electron-withdrawing group is reminiscent of the analogous circumstances in the Peterson carbonyl olefination, where a rearrangement of the silyl group (Scheme 63) is assumed for explaining the observed effect[91].—The triphenylstannyl group was also eliminated even at low temperature in the reaction of **71** with benzaldehyde[24e].



Scheme 63.

5.1.4. *Synthesis of Non-Terminal Olefins*

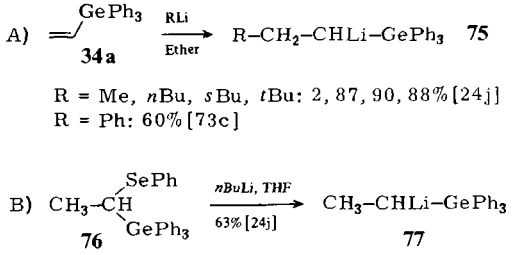
Extension of the carbonyl olefination with Sn- and Pb-reagents mentioned in Section 5.1.1 to the synthesis of non-terminal olefins appears less worthwhile, since compounds **72**, El = Sn, Pb, are relatively difficultly accessible (see Schemes 19 and 21) and the equilibria set up in the organoelement/Li exchange (Scheme 64) lie distinctly more unfavorably than in the corresponding methane-derivatives as a result of poorer charge-stabilization in **73** (see Table 1).



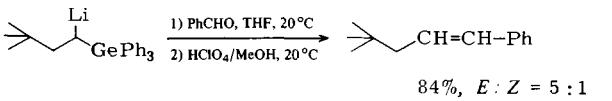
Scheme 64. *A*: 110°C, toluene, 22 h, 15% [24m]; *B*: $HClO_4$, ≈90% [24m].

Moreover, the β-hydroxy compounds, *e.g.* **74**, formed from carbonyl compounds and **73**, are thermally more stable than the corresponding compounds **59** (Scheme 55).

α-Lithiated triphenylgermylalkanes such as **75** and **77** are far more easily accessible than the analogous Sn- and Pb-compounds, namely by addition of organolithium compounds to triphenylgermylethene **34a** (Scheme 65 A) or *via* Se-compounds (*e.g.* according or analogous to Scheme 65 B; **76** is synthesized according to Scheme 18). Whether they offer advantages over the corresponding more cheaply available α-lithiated triphenyl- and trimethylsilylalkanes is still undecided. Presumably they—as well as the corresponding transition metal compounds of type **63** (cf. Table 13)—show enhanced nucleophilicity. The only carbonyl olefination carried out so far (Scheme 66) is promising with regard to yield and stereoselectivity.



Scheme 65.



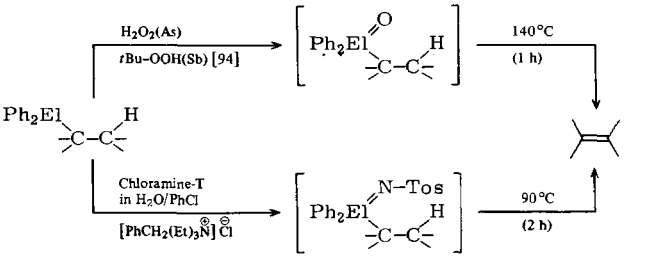
Scheme 66 [24j].

The synthetic routes formulated in Scheme 65 cannot be extended to the Sn- and Pb-analogues[92].

5.2. Elimination of Organoarsenic- and Organoantimony Groups together with β-H Atoms

The importance of organoselenium reagents in organic synthesis is largely based on the fact that selenium oxide groups are rapidly eliminated together with a β-H atom with formation of olefin, even at room temperature[55]. When the cleavage of seleno groups *via* the oxide (primary seleno groups) is rendered difficult, the phase-transfer reaction with chloroamine-T *via* selenium tosylimine has proven useful[93].

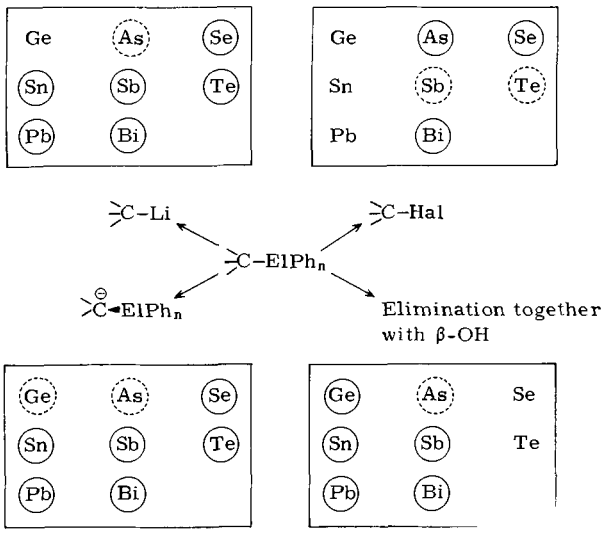
We extended both methods to primary diphenylarsino- and diphenylstibinoalkanes (Scheme 67) and found that the route *via* the oxide leads to olefin formation (*ca.* 21—23%) only in the case of the Sb-compounds, whereas the expected olefins are formed in both cases *via* the tosylimine. However, since the yields were unsatisfactory[24h] (El = As, 41-45%; El = Sb, 53-56%) and the required decomposition temperature (90°C) was relatively high, this method cannot be fully recommended. Surprisingly, in analogous reactions with a secondary arsane and stibane (2-diphenylarsinooctane[25a], 2-diphenylstibinopentane[12]) only minimal amounts of olefin could be detected.



Scheme 67, El = As, Sb [24h].

6. Conclusion and Outlook

On examining heavy main-group elements for possible uses in organic synthesis we found, in the case of the elements marked with a circle in Scheme 68, that there are four possible modes of reaction. As shown in Scheme 68, none of the elements investigated is completely unsuitable for synthetic application. Moreover, each element—even the inconvenient bismuth[18]—revealed special characteristics and useful features arising from a combination of various properties. The element Te, *e.g.*, is exceptionally good in that it has a strong acidifying effect in the functional group PhTe, it is the most amenable to organoelement/Li exchange, and it forms essentially more thermally stable α-hetero-substituted carbanions (cf. **4h** and **35h**) than the comparable elements Br and I (cf. **8**).



Scheme 68. Four possible reactions of organoelement compounds >C—ElPh$_n$.

The author is convinced that all the elements investigated here (selection criterion: see Section 1) will at some later date become trusted and profitable "heteroatoms" for the practising synthetic chemist. The element As, which, unlike the neighboring elements Si, P, S, Se in the Periodic System is rarely taken into consideration, has proven particularly useful for our research group. Because of its suitability as air-stable donor atom in transition-metal ligands it still plays a major role in new investigations being carried out by our group[95].

For the results presented here I am grateful to all those enthusiastic and capable colleagues who have been engaged in this work and who have also shown their professional prowess at handling toxic substances. I sincerely thank all colleagues cited in the references and hope that this report might bring back memories of their having joined in the combined effort as members of our research team studying organoelements. I also wish to thank Herrn H. Niewind, Organisch-chemisches Institut der Universität Münster, for the synthesis of numerous starting substances, as well as the Deutsche Forschungsgemeinschaft (Ka 144/34 and Ka 144/35-1), the Ministerium für Wissenschaft und Forschung des Landes Nordrhein-Westfalen (Project "Unreaktivierung durch Ummetallierung") and the Fonds der Chemischen Industrie for very helpful financial support.

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[30] The reaction **3c**→**4c** (Scheme 8, R = Ph), was practically quantitative, irrespective of whether 1 mmol of **3c** (Ph_3Pb does not precipitate) or 8 mmol of **3c** (Ph_3Pb precipitates) per 100 mL of THF were used [24m].

[31] Th. Kauffmann, A. Hamsen, R. Kriegesmann, A. Vahrenhorst, *Tetrahedron Lett. 1978*, 4395.

[32] Pure products could not be isolated according to the reaction of **4f** with aldehydes and organoelement halides, although **4f** was completely consumed.

[33] **10f** could be obtained (66%) from PhSeNa and **7d**. Reaction with *n*-BuLi leads to **4d** (45%) [24i]. – While organolithium compounds are activated by chelate ligands with hard donor centers, *e.g.* tetramethylenediamine (TMEDA), from our experience the reverse is the case with chelate ligands with soft donor centers.

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[36] The strong steric shielding of the nucleophilic center of **13c** results in α-H abstraction being the main reaction in the case of enolizable carbonyl compounds. For analogous observations see [20c].

[37] **12b** had been described in the literature on two previous occasions (C. A. Kraus, H. Eatough, *J. Am. Chem. Soc. 55* (1933) 5014; D. S. Matteson, R. J. Wilcsek, *J. Organomet. Chem. 57* (1973) 231), but according to m.p. or ^{1}H-NMR data it was not **12b** (m.p. 181 °C) in either of the two cases.

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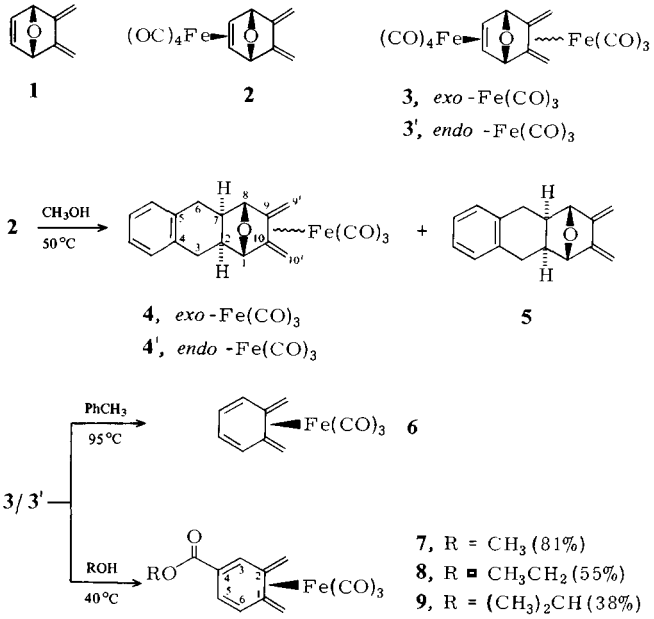
Carbonyliron-Assisted Cycloaddition of a 1,3-Diene to a CC Double Bond: Synthesis of an Anthracyclinone Precursor**

By *Philippe Vioget, Pierre Vogel,* and *Raymond Roulet**

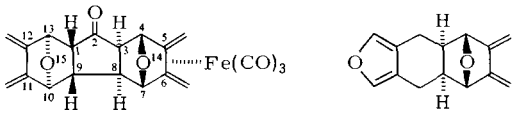
The cycloaddition of a 1,3-diene to a monoolefin coordinated to a transition metal has not been reported so far. The reaction is unfavored as the final cyclohexene complex would be coordinatively unsaturated[1]. It can occur, however, if the required extra ligand is incorporated into the dienophile[2] or if the dienophile is a CC triple bond[3]. We report the first case of a formal [4+2] cycloaddition in which the dienophile is complexed by carbonyliron, namely the cyclodimerization of 5,6-bismethylene-7-oxabicyclo[2.2.1]hept-2-ene **1** in presence of $Fe_2(CO)_9$, the extra ligand being probably the oxygen bridge of the oxanorbornene system.

The reaction between **1** and $Fe_2(CO)_9$ in pentane yields the mono- and dimetallic complexes **2**, **3** and **3'**[4]. In methanol at 50 °C, the complexes **4** and **4'** (30%, yellow crystals, m.p. = 128–129 and 175–177 °C, respectively), the diene **5** (9.3%; colorless crystals; m.p. = 130–131 °C; ^{1}H-NMR (360 MHz, $CDCl_3$, TMS): δ = 7.13 (m, 4H), 5.22/4.98 (2s, 2×2H, =CH_2), 4.61 (s, 2H, H-1,8), 2.90/2.57/2.16 (3 m, 3×2H, ^2J = 13.5 Hz, ^3J = 5.0 and 9.0 Hz); ^{13}C-NMR (90.55 MHz, $CDCl_3$, TMS): δ = 148.0/138.4 (2s), 126.9 (dd, ^1J(CH) = 154 Hz, ^3J = 5 Hz); 126.3 (dd, ^1J = 159 Hz, ^3J = 9 Hz), 101.0 (t, 160 Hz), 86.7 (d, 154 Hz), 44.8 (d, 137 Hz), 32.3 (t, 128 Hz)), and the *ortho*-quinodimethane complexes **6** (6.5%) and **7** (3%) were formed. Heating **2** in methanol (50 °C) gave **4** (33%), **5** (11%), and **6** (14%). Thermolysis of **3** in toluene gave **6** (60%)[4]. Heating **3** in methanol, ethanol, and 2-propanol gave the esters **7**–**9**. Control experiments confirmed that the cyclodimerization



1 **2** **3**, *exo*-$Fe(CO)_3$ **3'**, *endo*-$Fe(CO)_3$ **4**, *exo*-$Fe(CO)_3$ **4'**, *endo*-$Fe(CO)_3$ **5** **6** **7**, R = CH_3 (81%) **8**, R = CH_3CH_2 (55%) **9**, R = $(CH_3)_2CH$ (38%)

occurred only with the monometallic complex **2**. Oxidation of **4** and **4'** by $(CH_3)_3NO$ in acetone furnished **5** (98%, relative to **2**: 41%). The coupling constant $J_{1\text{-H},2\text{-H}} \simeq 0$ Hz in **4**, **4'**, and **5** confirmed the *exo*-annelation.



10 **11**

Irradiation of **1** in CH_3OH in presence of $Fe_2(CO)_9$ at −20 °C results in formation of the cyclopentanone derivative **10**: reaction of **1** and $Ru_3(CO)_{12}$ in toluene (65 °C, 7 d) results in isolation of the furan **11** in 10% yield, in addition to 10% of **5**.

The reaction sequence **2**→**4**→**5** gives a simple route to the synthesis of bismethylene compounds **5**, a potential precursor for the preparation of antitumor agent 4-demethoxydaunomycinone[8].

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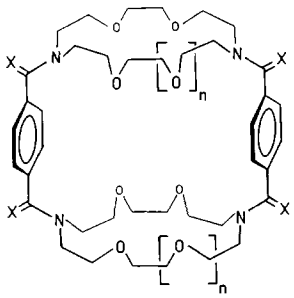
A Ternary Clathrate from Cryptand, Hydroquinone and Water — Selective Formation and X-Ray Structural Analysis**

By *Fritz Vögtle**, *Heinrich Puff*, *Edmund Friedrichs*, and *Walter M. Müller*

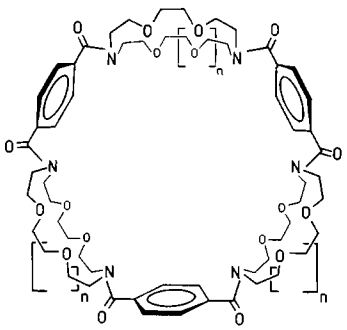
Dedicated to Professor Hermann Stetter on the occasion of his 65th birthday

In the last few years it has been possible to prepare numerous (neutral) complexes of crown ethers with uncharged guest molecules[1]. We describe here for the first time the synthesis and X-ray structural analysis of a ternary neutral complex of an uncharged cryptand compound - with hydroquinone and water.

The host molecules **1a** (m.p. = 216—220 °C)[2a] and **2a** (m.p. = 89—93 °C), which are similar to cyclodextrins in their cavity size and water solubility, were obtained by reaction of terephthaloyl dichloride with 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane under conditions of high dilution.



1a: X=O n=1
1b: X=H_2 n=1



2a: n=1
2b: n=2

The 32-membered tetralactam **1a**, which was recrystallized from water, still retained water after being dried for 12 h (12 torr, 50 °C), forms a 1 : 1 : 4 complex in water with hydroquinone[4] (**1a**: hydroquinone:H_2O; m.p. = 185—187 °C) even if the ratio of hydroquinone: cryptand in water is 2 : 1. The ready solvation of hydroquinone in hot chloroform ("neutral phase transfer"[4]) and the stabilization of the hydroquinone solutions from oxidation by **1a** indicate that complexation occurs even in solution.

Hydroquinone was isolated from aqueous solutions of quinhydrone *via* complexation with **1a**. **1a** also yields a crystalline complex with resorcinol, although more slowly, and with pyrocatechol even more slowly. From the mixture of these three benzenediols with 0.3 equivalents **1a**, only the hydroquinone complex precipitates. This can be exploited for a preparative separation.

The X-ray structure analysis of the 1 : 1 : 4 complex (Fig. 2) indicates that the hydroquinone is not incorporated into the cavity of the cryptand, although in this position it could complex with the crown ether moieties[4]. Apparently the bonding of the hydroquinone molecules outside the cryptand *via* H bonds involving water molecules leads to a more stable crystal lattice. Of note is the fact that the H bonds are formed exclusively with the carbonyl oxygen atoms of the cryptand.

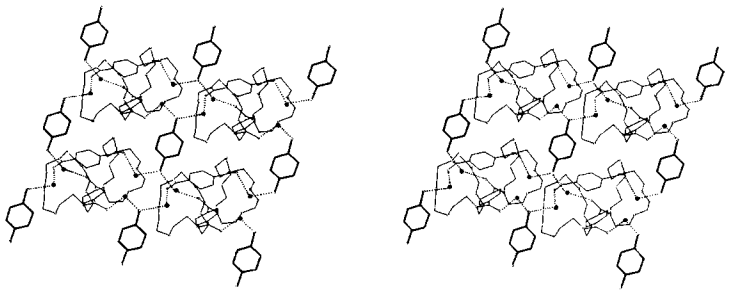


Fig. 2. Structure of the **1a**-hydroquinone-H_2O clathrate (1 : 1 : 4) in the crystal; section of one layer (stereoscopic view).

The lattice consists of layers of hydroquinone, water, and cryptand. The triclinic unit cell with $a = 10.427(6)$, $b = 12.842(5)$, $c = 18.908(7)$ Å, $\alpha = 91.99(3)$, $\beta = 98.83(4)$, $\gamma = 94.44(4)°$, and space group $P\bar{1}$ contains 2 molecules of hydroquinone and cryptand, respectively, and 8 molecules of water[5a].

Guest molecules such as 1,2,4-, 1,3,5-, and 1,2,3-benzenetriols as well as 2,7-naphthalenediol, which have similar spatial demands as hydroquinone, also yield stable isolable 1 : 1 : n H_2O-complexes; 2,6-naphthalenediol, 4-nitrophenol, 4-hydroxybenzyl alcohol, and similar compounds do not form crystalline complexes.

The water-insoluble amine **1b** (m.p. = 111—113 °C), as well as water-soluble and -insoluble analogues of **1a** do not afford complexes of this type under the same conditions.

The 48-membered hexalactam **2a**, which is also water-soluble, has a larger cavity than γ-cyclodextrin. In this case, aqueous solutions of 1,3,5-benzenetricarboxylic acid and benzenehexacarboxylic acid are suitable guest compounds; crystalline complexes (m.p. 237—245 °C and 166—173 °C, respectively) could be isolated, but their structures have not yet been determined.

From these results it can be concluded that even with cyclodextrin-analogous uncharged and water-soluble host compounds such as **1a** a guest molecule which fits into the cavity must not necessarily be incorporated even when H-bonding contributes to stabilization. As shown in the example of the 1 : 1 : 4 complex, the lattice-clathrate formation—which also occurs in cyclodextrins—competes successfully.

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[5] a) Details of the crystal structure study can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, F.R.G., by quoting the name of the author and a complete citation of the article.

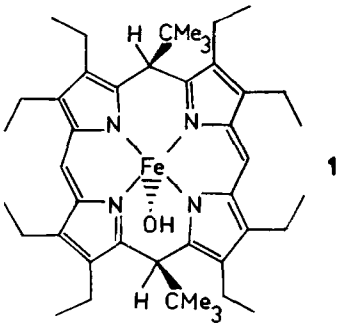
A Mononuclear Hydroxoiron(III) Complex of a Porphinoid Ligand System with Bifacial Steric Hindrance**

By *Johann W. Buchler**, *K. Lam Lay*, *Young J. Lee*, and *W. Robert Scheidt**

Mononuclear hydroxoiron(III) porphyrins are normally unstable, the ease of condensation of isolated FeOH groups to FeOFe bridges preventing their isolation[2]. Recently, a variety of mononuclear hydroxohemins have been mentioned, the stability of which is attributed to bifacial steric hindrance, *i.e.* to bulky substituents on both sides of the porphinato plane[2,4]. The published data of these compounds do not yet allow full characterization.

We report here a well-defined mononuclear hydroxoiron(III) complex of a porphinoid ligand system: [α,γ-bis(*tert*-butyl)-octaethyl-α,γ-dihydroporphinato]hydroxoiron(III) **1**, an iron α,γ-dialkylporphodimethene.

The synthesis of **1** is achieved by reductive *tert*-butylation of octaethylporphinatozinc, demetalation of the product, iron insertion, and exhaustive chromatography on alumina by analogy to [5] (for details see [6c]).



1

Under basic conditions, condensation of **1** to afford a μ-oxo complex does not occur. However, even traces of alcohols lead to formation of the previously disregarded[4] alkoxo complexes, which are recognized by rhombic ESR spectra, whereas **1** has an axial spectrum ($g_\perp = 5.84$, $g_\parallel = 2.00$).

The configuration of **1** as its dimethylacetamide solvate was determined by X-ray structure analysis (Fig. 1). The essential structural parameters (Fe—O, 188.6(1.0), Fe—N, 204.4(3.0) pm, and the displacement of the Fe atom from the plane of the four N atoms by 40 pm in the direction of the OH group) are consistent with those expected for a high-spin iron(III) porphinate[9]. The two halves of the macrocycle are folded in a roof-like manner (dihedral angle 42.9°). The two *tert*-butyl groups occupy "chimney positions" on the ridge of the roof, similar to the positions of the methyl groups in the previously characterized α,γ-dimethylporphodimethene derivatives[2].

A quite surprising feature is the *anti*-axial configuration of the two *tert*-butyl groups and the hydroxo ligand. Obviously, the two *tert*-butyl groups prevent any binding of a ligand to the *syn*-axial position, although in some related α,γ-dimethylporphodimethene complexes of pentacoordinate metal ions, *e.g.* the titanyl ion, the *syn*-axial position is preferred[2].

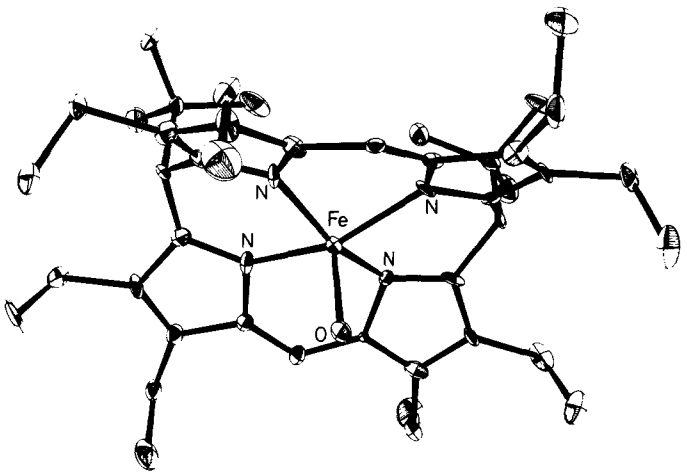


Fig. 1. *Anti*-axial configuration of the mononuclear hydroxoiron(III) porphodimethene **1** in the crystal [8] (viewed from below the roof).

Since the condensation of two molecules of **1** to afford a μ-oxo complex does not occur, although the *tert*-butyl groups do not impede the hydroxo ligand, it follows that the α,γ-bis(*tert*-butyl)porphodimethene skeleton provides bifacial steric hindrance, resulting, on the one hand, from the bulky *tert*-butyl groups and, on the other from the folding of the macrocycle: this does not even permit formation of a greatly over-extended Fe—O—Fe bridge at the *endo*-side. This type of steric hindrance provides interesting modifications to reactions of small molecules with hemes derived from **1**, and this is presently being investigated.

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Polarity of Organic Glasses**

By *Heinz Langhals**

Empirical polarity scales are usually used for the quantitative description of solvent polarity, since purely physical solvent properties such as refractive index or dielectric

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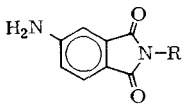
constant are unsatisfactory parameters for most chemical applications[2].

The empirical *Y*-scale developed by *Winstein*, which is based on solvolysis reactions, presently serves as a general reference system. However, it is limited to polar media, whereas the secondary polarity scales derived from spectroscopic data and linearly correlating with the *Y*-scale, *e.g.* the $E_T(30)$ scale of *Dimroth* and *Reichardt*, can also be applied in low polarity media.

The empirical polarity quantities are defined only for the liquid phase; it should be checked, however, as to how far an extension to solids is possible (see also [4]). The phthalimides **1** and **2**, which are also readily soluble in



1, R = CH_3; S_1
2, R = H; S_2

low polarity media and, with their strong solvatochromism in the fluorescence, are sensitive to polar solvation effects, can be used as models here.

$$S = 28\,590\ [\text{kcal}\cdot\text{nm}\cdot\text{mol}^{-1}]\ \lambda_{max}^{-1} \qquad (1)$$

The molar emission energy S is calculated analogously to the E_T values, from λ_{max} of the fluorescence using eq. (1); S correlates linearly with the $E_T(30)$ scale.

$$E_T(30) = -1.93\,S_1 + 160.4$$
$$E_T(30) = -1.81\,S_2 + 155.7$$

Organic glasses, *e.g.* polymethylmethacrylate (Plexiglas) are suitable model solids for the investigation of polarity, since their spatial isotropism favors accuracy of measurement. We found that pure Plexiglas prepared by melting granules shows only low polarity ($E_T(30) = 37.3$) at 25 °C, comparable to 1-chloropropane. Even a small residual content of monomer noticeably increases the polarity; it can be increased into the polarity range of 2-butanol ($E_T(30) = 47.5$) by addition of *ca.* 10% methanol.

Accordingly, solvatochromic dyes are just as influenced by the medium in organic glasses as in liquids. That the solvatochromism of the fluorescence of **1** or **2** in the glasses investigated actually reflects the polarity of the medium can be shown with eq. (2),

$$S = E_D \ln(c_p/c^* + 1) + S^0 \qquad (2)$$

which quantitatively describes the polar behavior of binary liquid mixtures[10]. c_p is the molar concentration of the more polar component and S^0 the S-value of the less polar component (here pure Plexiglas). E_D and c^* are the parameters of the equation.

Equation 2 also describes the polar behavior of solid mixtures and holds both for solid copolymers (examples see Fig. 1) as well as for low molecular additives to polymers (1,2-propanediol and 1,3-butanediol).

This finding is of interest for the directed preparation of polymers having definite properties, for an understanding of the action of softeners, and for the analysis of polymers. It follows from these findings that the polarity of solid matrices can be defined empirically in the same way as the polarity of liquids (for a summary of previous works see[13]).

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CAS Registry numbers:
1, 2307-00-8; **2**, 3676-85-5; plexiglas, 76416-69-8.

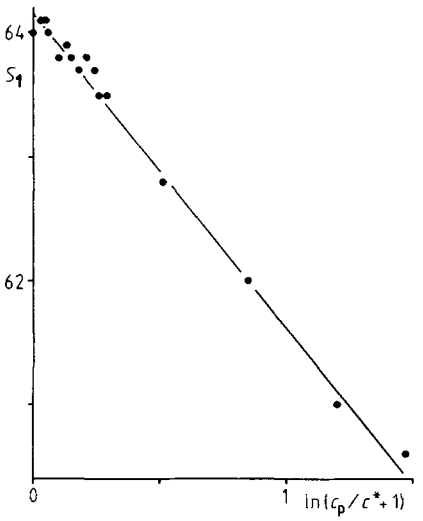

Fig. 1. Linear relationship between S_1 (dye **1**) and $\ln(c_p/c^*+1)$ according to eq. (2) for the copolymer of methyl methacrylate and 2-hydroxypropyl methacrylate.

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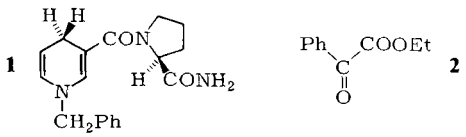
Dependence of the Enantioselectivity on the Relative Concentration of Substrate in an NADH Model Reaction**

By *Naomichi Baba*, *Jun'ichi Oda*, and *Yuzo Inouye**

Recently we found[1] that the NADH model system **1**, which contains L-prolinamide as a chirality-inducing center, reduced ethyl 2-oxo-2-phenylacetate **2** (in presence of $Mg(ClO_4)_2$ at 50 °C in anhydrous CH_3CN) to give (*R*)-ethyl mandelate in high enantiomeric excess (*e.e.* = 83%)[1] and that the *e.e.* increased as the reaction proceeded. A similar increase has also been reported in other examples[2] and was accounted for in terms of the feedback effect of the oxidized nicotinamide, which accumulates during the



conversion (Scheme 1): the oxidized form **4** interacts ("feedback interaction") with the reductant **3** *via* chelative mediation of metal ion and/or charge transfer interaction. This may bring about specific blocking of one of the diastereotopic faces of the dihydropyridine ring (chiral selection), permitting easier access of the substrate carbonyl

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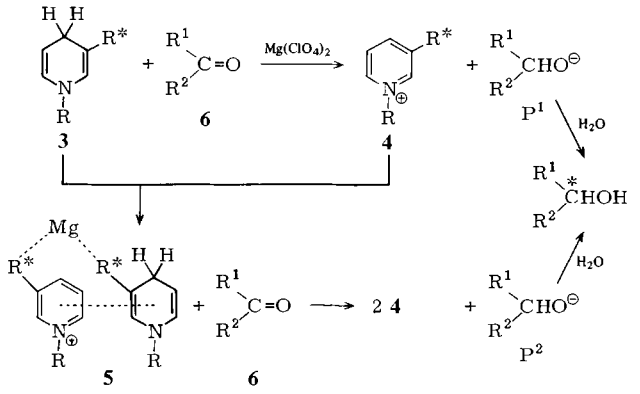
compound to the other face, and thereby contributing much towards increasing the enantiomeric excess in the later stages of the reduction.



Scheme 1. Hypothetical pathway of the asymmetric reduction with nicotinamide derivatives **3** using a feedback interaction between **3** and **4**.

The feedback mechanism can be described by eqs. (a)—(c):

$$A + S \xrightarrow{k_1} C + P^1 \quad (a)$$

$$B + S \xrightarrow{k_2} 2C + P^2 \quad (b)$$

$$A + C \xrightarrow{k_3} B \quad (c)$$

where A = Mg^{2+}-activated[6], chiral NADH model **3**; C = oxidized species **4**; B = hypothetical intermediate **5**; S = substrate **6**; P = product. The *e.e.* can be calculated using eq. (d):

$$e.e. = \frac{(m-n)K + m - (n-m)JK(1-[S]/[S_0])^{-1}\ln[([S]/[S_0]+K)(1+K)^{-1}]}{} \quad (d)$$

where, m and n represent the optical yield of P^1 and P^2, respectively, with the assumption that $n > m$; $J = k_1(k_1-k_3)^{-1}$ and $K = k_3(k_1-k_3)^{-1}$. Eq. (d) shows that the *e.e.* should increase monotonically with increasing initial concentration of the substrate ($[S_0]$); moreover, as is found, an increase in *e.e.* is also to be expected with decreasing $[S]$ towards the end of the reaction.

In accord with predictions, a significant increment in *e.e.* (from 46 to 76%) was observed in the reduction of **2** upon increase of the substrate initial concentration from 10^{-2} to 10^{-1} M.

This constitutes the first example in which the enantioselectivity is dependent on the initial concentration of substrate. It seems very likely that a similar feedback interaction between products and reactants may sometimes be operative in other asymmetric systems. Accordingly, it might possibly be used as a probe for studying the mechanisms of other reactions.

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Photochemical Evolution of H_2 in the System Methyl Viologen/Mn^{II}-*meso*-Tetraphenylporphyrintrisulfonic Acid/Mercaptoethanol/Hydrogenase**

By *Ichiro Okura**, *Nguyen Kim-Thuan*, and *Makoto Takeuchi*

Aside from zinc porphyrin complexes[2] almost exclusively ruthenium complexes have been used as sensitizers in studies on the photo-induced cleavage of water[1]. We report here on the use of the manganese(II) *meso*-tetraphenylporphyrintrisulfonic acid complex (Mn^{II}-TPP(SO_3H)$_3$) as photosensitizer for the photo-induced reduction of methyl viologen (*N,N'*-dimethylbipyridinium dichloride, MV^{2+}); photochemically facile redox reactions are possible with manganese porphyrin and phthalocyanin complexes[3]. Since the reduced form of methyl viologen (MV^+) in the presence of a catalyst liberates H_2 from water, we attempted carrying out this reaction with the system Mn^{II}-TPP(SO_3H)$_3$/MV^{2+}/mercaptoethanol/hydrogenase.

Mn^{II}TPP(SO_3H)$_3$ was generated *in situ* from the corresponding Mn^{III} complex, which was synthesized from TPP(SO_3H)$_3$ and Mn(OAc)$_3$ in CH_3OH. The hydrogenase from *D. vulgaris* was purified according to *Yagi*'s method[4]; the hydrogenase solution had the ability to generate 8.5×10^{-7} mol of hydrogen using the reaction system: hydrogenase (0.1 mL) + MV^{2+} (8.1×10^{-7} mol) + $Na_2S_2O_4$ (2×10^{-5} mol) in 3 mL of a 0.02 M phosphate buffer (pH 7) at 30 °C for 20 min. Irradiation (150 W tungsten lamp, $\lambda > 390$ nm) of a buffered (Tris-HCl, pH 7) aqueous solution of Mn^{III}-TPP(SO_3H)$_3$, MV^{2+}, and mercaptoethanol under anaerobic conditions at 30 °C led to formation of MV^+ (characteristic absorption at 395 and 605 nm); as shown in Figure 1 the formation of MV^+ first sets in after an induction period, and then increases with time. During the induction period the concentration of Mn^{III}-TPP(SO_3H)$_3$ drops rapidly (rapid decrease in intensity of the band at $\lambda = 467$ nm), with concomitant formation of Mn^{II}-TPP(SO_3H)$_3$, which shows a strong absorption at $\lambda = 435$ nm: Aeration (introduction of oxygen) leads to immediate reconversion of the Mn^{II}-complex into the Mn^{III}-complex.

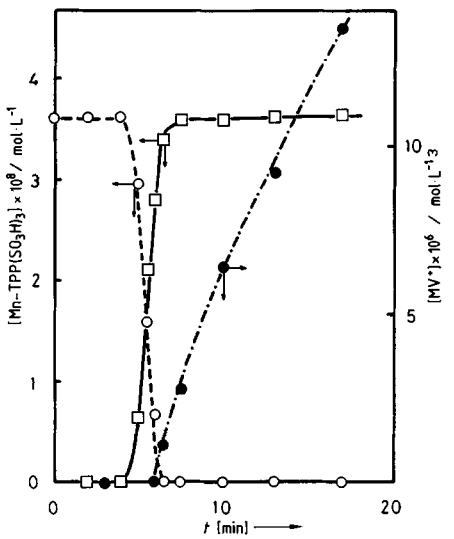

Fig. 1. Change of concentration of Mn^{III}-TPP(SO_3H)$_3$ (○), Mn^{II}-TPP(SO_3H)$_3$ (□), and MV^+ (●) on irradiation of 6 mL of an aqueous solution of 1.31×10^{-9} mol Mn^{III}-TPP(SO_3H)$_3$, 8.12×10^{-7} mol MV^{2+}, and 5.43×10^{-4} mol mercaptoethanol at 30 °C.

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When hydrogenase (0.5 mL) was added to the buffered aqueous (6 mL) system Mn^{III}-TPP$(SO_3H)_3$ (4.64×10^{-9} mol), MV^{2+} (7.26×10^{-6} mol) and mercaptoethanol (5.43×10^{-4} mol), evolution of hydrogen was observed on irradiation: the amount of hydrogen evolved after 2 h and 4 h was 1.23 μmol and 1.89 μmol, respectively. No evolution of hydrogen was observed when any component of the system was omitted. Hydrogen evolution (1.08 μmol H_2 in 4 h) was also observed on irradiation with sunlight instead of with a tungsten lamp.

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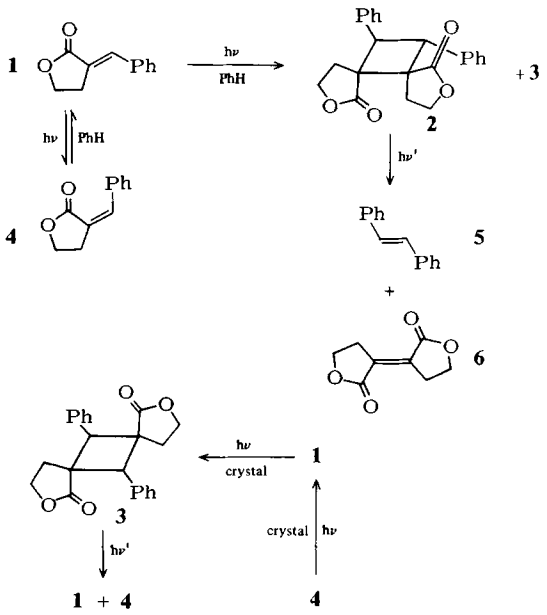
Quantitative Photodimerization of Crystalline α-Benzylidene-γ-butyrolactone**

By *Gerd Kaupp**, *Ernst Jostkleigrewe*, and *Hans-Jörg Hermann*

The lactone **1** (m.p. = 115–116 °C), which is readily accessible from γ-butyrolactone and benzaldehyde[1], is of importance as a fungicide and plant growth regulator[2]. The photochemistry of **1** (*trans/cis*-isomerization; solvent addition) has given rise to extensive theoretical speculations[3]. We have now found that **1** photodimerizes in solution and in the crystalline state.

Irradiation of **1** in benzene (Hg high-pressure lamp, Hanovia, 450 W; Solidex filter, N_2, 1 g, 3 d, 37% conversion) results in formation of **4** (16%), **2** (12%; isolated *via* preparative thin layer chromatography on SiO_2 with CH_2Cl_2, m.p. = 170 °C), **3** (4%), and an unidentified compound (*ca.* 5%; ^{1}H-NMR analysis). On the other hand, photolysis of crystalline **1** proceeds rapidly and quantitatively (1 g is converted in 5 h) without the formation of **4** (cf. [4]). The head/tail *anti*-dimer **3** is formed exclusively under these conditions, and is obtained analytically pure after one crystallization from CCl_4 (m.p. = 242 °C). In accordance with the *cis*-effect[5], photolysis of the dimers **2** and **3** (253.7 nm, 83 K) results predominantly in formation of **5**[5a] and **6**[5b], and of **1** and **4** (both orientations!), respectively. The symmetry of the stereoisomers **2** and **3** was established from the 250 MHz ^{1}H-NMR spectra[6].



The perfectly regio- and stereospecific as well as rapid and quantitative course of the photolysis of the crystalline lactone **1** is noteworthy, since other benzylidene compounds can give rise to several photodimers without melting[4]. The specificity is so pronounced here, that upon photolysis (as above) of crystalline **4**, (m.p. = 90 °C[3]; rarely observed *Z/E*-isomerization in the crystal!) even intermediately generated and ^{1}H-NMR-spectroscopically detected **1** dimerizes exclusively to give **3**.

In addition to the crystallochemical aspects, the particularly facile preparative accessibility to **3** appears attractive. Corresponding to the procedure in [4], the crystal film of the educt **1** may be generated, without particular precautions, by evaporation of its solutions (*e.g.* in dichloromethane) or by solidification of its melt, and may be irradiated without exclusion of air. Therefore, exposing finely divided crystal films of the biologically active[2] **1** to sunlight (the short wavelength portion of which is absorbed by **1**[3]) appears worthy of more detailed studies.

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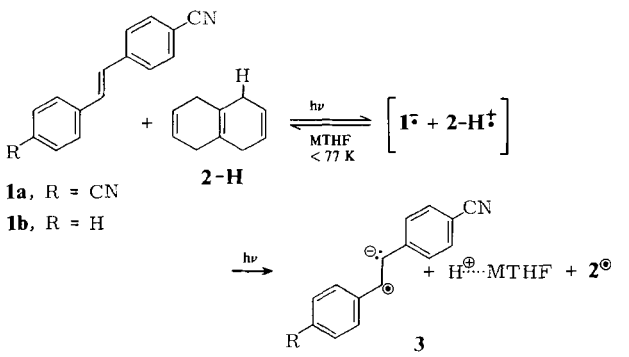
[6] ^{1}H-NMR ($CDCl_3$): **2**: $\delta = 7.39-7.18$ (10H); 4.47 (2H, s); 4.16 (2H, ddd, $J = 9; 9; 2$); 3.99 (2H, ddd, $J = 11; 9; 6$); 2.77 (2H, ddd, $J = 14; 6; 2$); 1.98 (2H, ddd, $J = 14; 11; 9$); **3**: 7.43—7.28 (10H); 4.39 (2H, s); 4.20 (2H, br. ddd, $J = 9; 8.5$; ca. 0.5); 4.04 (2H, ddd, $J = 11.5; 9; 5$); 2.83 (2H, br. ddd, $J = 13; 5$; ca. 0.5); 2.26 (2H, ddd, $J = 13; 11.5; 8.5$ Hz).

Laser Photolysis— A New Route for Charge Separation**

By *Gerd Kaupp** and *Ernst Jostkleigrewe*

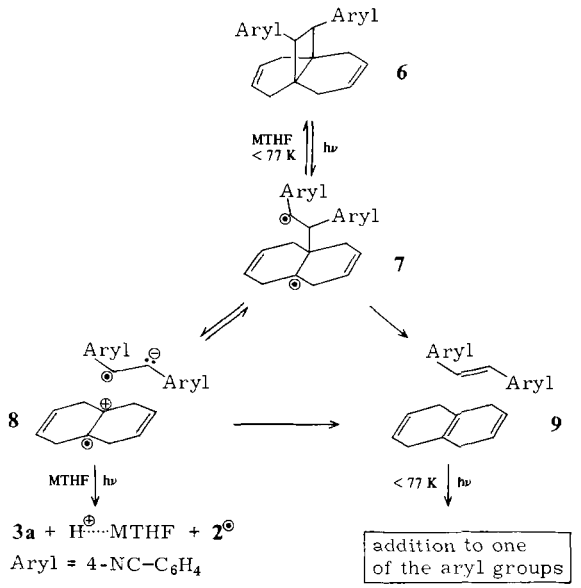
While photoionization to give stable radical cations causes no problems, photochemical charge-separation to give stable radical anions and (secondary) cations, which is potentially useful for storage of light energy, has met with enormous difficulties[2]. We report on a new technique, which successfully forms charge separations *via* photodeprotonation of radical-ion pairs.

Upon irradiation of **1** at 15—77 K in a polar 2-methyltetrahydrofuran (MTHF) glass, preferentially in presence of additional electron donors such as **2-H** (or toluence, or triethylamine), the VIS-spectra of the radical anions **3** are obtained only if pulsed short-wavelength light sources (60—250 or ≥ 10 mJ nanosecond pulses from an excimer laser at 248 or from the stimulated Raman emission of H_2 at 277 nm) are used. Under these conditions the radical cation **2-H**$^+$, which is formed *via* electron transfer and is paired with **1**$^-$, can immediately absorb light[4] and thus undergo photodeprotonation. **3a** ($\lambda_{max} = 567$, 545 (sh), 505 (sh) nm) and **3b** ($\lambda_{max} = 517.5$, 485, 440 nm) are not formed upon pulsed excitation at 355 nm (*ca.* 10 mJ, dye laser) or upon continuous irradiation with 15 W low-pressure Hg lamps.



Evidently, "spontaneous" deprotonation of **2-H**$^+$ (or the radical cations of toluene and triethylamine) with channeling of the proton out of the ion-pair cage[2b] is too slow here for successful competition with the back-transfer of the electron (to give **1** + **2-H**). Correspondingly, the spectrum of the radical anion of 4,4'-dicyanoacetylene ($\lambda_{max} = 499$, 481.5 nm) is obtained only after pulsed laser excitation (248 nm, with **2-H** in MTHF glasses).

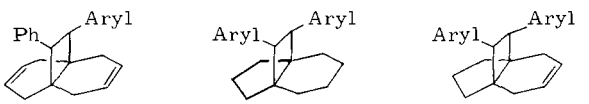
The new charge-separation technique also permits the spectroscopic detection of stable radical anions in cycloreversions (as competing reaction). Thus, only pulsed laser excitation (248; 277 nm) of **6** in MTHF at 15—77 K yields the VIS spectrum of **3a**. Here also, the "removal" of the positive charge has to be accelerated by additional absorption of light and photodeprotonation of the radical cation, if stable **3a** is to be formed in competition with cycloreversion of **7** (which is reformed in part from **8**) and charge transfer in **8**.



The radical anions **3a** and **3b** generated from **1**, **6**, or **10** are stable below the softening range of the glass at 95—100 K. However, short wavelength irradiation (253.7 nm or over-irradiation with the laser) rapidly bleaches the red color (presumably *via* "photodetachment"[5]), but even intense long wavelength excitation (high-pressure Hg lamp at $\lambda = 546$, or pulsed at 567, 517.5, or 427 nm) does not cause electron transfer in the polar glass. The radical anion of 4,4'-dicyanoacetylene behaves similarly.

The charge separation is not due to specific properties of exciplexes: Thus, irradiation ($\lambda = 365$ or pulsed at 377 or 360 nm) of the charge-transfer complex **9**, which is obtained at 15—77 K upon irradiation of **6** at $\lambda = 253.7$ nm, does not produce **3a** but rapidly diminishes the bathochromically shifted UV spectrum of **1a** in favor of new absorptions at $\lambda_{max} = 300$ and 280 nm. This corresponds to a shortening of the chromophore in **1a** by one 4-cyanophenyl group (*via* H_2 transfer from or cycloaddition with **2-H**).

The cycloreversion variant of the charge-separation technique gives the better yields of **3**, particularly upon excitation at 277 nm. In accordance with the formulated



10 **11** **12**

Aryl = 4-NC-C_6H_4

mechanism, the radical anions form with increasing ease along the series **10**, **11**, **12**, and **6**.

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Angew. Chem. Suppl. 1982, 1089-1099

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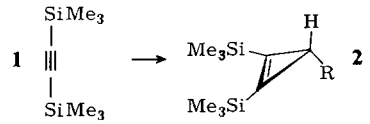
Synthesis and Properties of [2,3-Bis(trimethylsilyl)-2-cyclopropen-1-yl]-diazomethane**

By *Günther Maier**, *Manfred Hoppe*, *Hans Peter Reisenauer*, and *Carl Krüger*

Substituted cyclopropenyldiazomethanes — potential precursors of tetrahedranes — have been studied many times. So far, it is not known how a cyclopropenylcarbene behaves in argon at 10 K. In order to reduce the synthetic difficulties we have chosen the trimethylsilyl analogues, in the hope that the protecting groups could be removed at the end of the synthetic sequence[4].

The CuBr-catalyzed thermolysis of methyl diazoacetate in presence of bis(trimethylsilyl)acetylene **1** affords the cyclopropenecarboxylic acid ester **2a**[6]. Reduction with diisobutylaluminium hydride leads to alcohol **2b** and subsequent oxidation with silver carbonate/celite to aldehyde **2c**. Condensation with tosylhydrazide smoothly yields tosylhydrazone **2d** (Table 1), which reacts with butyllithium to furnish salt **2e**.



2a, R = CO_2Me; **2b**, R = CH_2OH; **2c**, R = CHO;
2d, R = CH=N–NHTos; **2e**, R = CH=N–NLiTos; **2f**, R = CHN_2

Table 1. (Selection) **2a—2d**: Yields, physical and spectroscopic properties; ^{1}H-NMR ($CDCl_3$; δ-values rel. to TMS). All substances gave correct elemental analyses.

2a: 18%, oil [6]; ^{1}H-NMR: 0.23 (s, 18H), 1.86 (s, 1H), 3.64 (s, 3H)

2b: 90%; oil; b.p. = 100°C/15 torr; ^{1}H-NMR: 0.20 (s, 18H), 1.47 (t, 1H, J = 5 Hz), 1.0—1.5 (br. s, OH), 3.41 (d, 2H, J = 5 Hz)

2c: 73%; oil; b.p. = 97°C/15 torr; ^{1}H-NMR: 0.13 (s, 18H), 2.15 (d, 1H, J = 8 Hz), 8.57 (d, 1H, J = 8 Hz)

2d: 69%; m.p. = 138—140°C (*E*/*Z*-mixture); ^{1}H-NMR: 0.13 (s, 18H), 1.84/2.00 (d, 1H, J = 8 Hz), 2.43 (s, 3H), 5.87/6.52 (d, 1H, J = 8 Hz), 7.15—8.00 (AA'BB', 4H)

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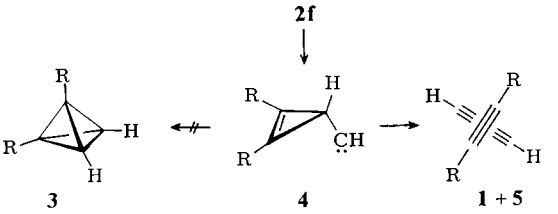
[**] Small Rings, Part 43. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 42. G. Maier, T. Sayraç, H. P. Reisenauer, *Chem. Ber.*, in press. - Details of the crystal structure study of **2f** can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, by quoting the number CSD 50189, the name of the author and a complete citation of the article.

Heating **2e** to 110°C in an oven flanged onto the vacuum mantel of a cryostat results in formation of the diazo compound **2f**, which can be condensed with argon onto a window at 10 K and subsequently cleaved photochemically (λ = 366 nm). The experiment shows that the initially formed carbene **4** does not participate in intramolecular addition to afford tetrahedrane **3** but decomposes even under the matrix conditions to yield the fragments **1** and **5**. Desilylated **2d** could not be converted into the corresponding diazomethane.



R = $SiMe_3$

In the CuBr-catalyzed reaction of **1** with methyl diazoacetate, apart from **2a** a colorless solid product is formed which decomposes only above 110°C and is shown from the X-ray structure analysis to be a π complex between CuBr and **1**. **1**·CuBr can be obtained without difficulty as long, colorless needles; this is consistent with the considerable readiness of **1** to form complexes with other transition metals[10].

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Radical Ion-Pairs as Intermediates in Reactions of Tetra-*tert*-butyltetrahedrane and Tetra-*tert*-butylcyclobutadiene**

By *Günther Maier**, *Klaus-Albert Schneider*, *Klaus-Dieter Malsch*, *Hermann Irngartinger*, and *Andrea Lenz*

Under normal conditions tetra-*tert*-butyltetrahedrane **1** is stable in air[1], whereas tetra-*tert*-butylcyclobutadiene **3** reacts readily with oxygen or water[2]. However, as soon as an acceptor is added **1** becomes very reactive. This effect can be illustrated by the two following examples.

Formation of the "Diels-Alder type" adduct **2** *via* a radical ion pair: Whereas **3**, despite the large steric hindrance, undergoes a diene addition with acetylenedicarboxylic ester[8], **1** remains unchanged under these conditions. When

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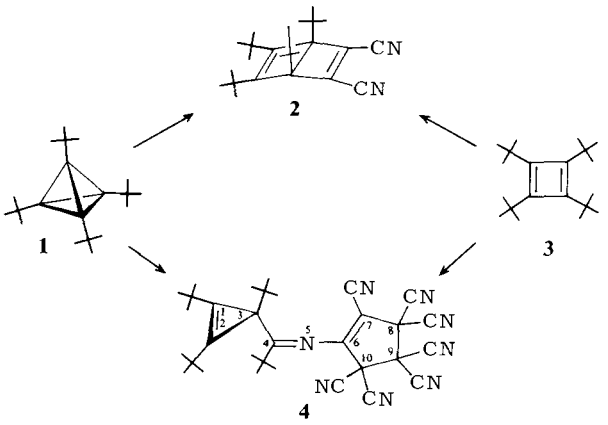
[**] Small rings, Part 44. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 43: G. Maier, M. Hoppe, H. P. Reisenauer, C. Krüger, *Angew. Chem. 94* (1982) 445, *Angew. Chem. Int. Ed. Engl. 21* (1981) 437.



dicyanoacetylene is used, however, both **1** and **3** yield the formal Diels-Alder adduct **2**. The following explanation is proposed: the oxidation potential of dicyanoacetylene is sufficient to generate the radical cation **5** from **1** and **3**. Recombination with the radical anion **6** thus formed leads to zwitterion **7**, which cyclizes to **2** (Table 1).

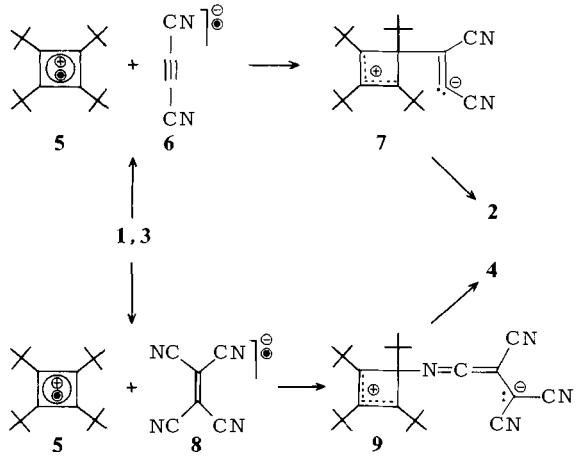


Table 1. (Selection). **2** and **4**: Yields, physical and spectroscopic properties; IR (KI) [cm^{-1}]; NMR ($CDCl_3$, δ-value rel. TMS, p = primary, q = quaternary). Both substances gave correct elemental analyses.

2: 74% from **1**, 63% from **3**; m.p.: 229 °C; IR: 2210 (C≡N), 1610 (C=C); ^{1}H-NMR: 1.41 (s, 18 H), 1.38 (s, 18 H)

4: quant. from **1** or **3** (NMR-spectroscopic; considerable losses on purification), m.p. = 100 °C (decomp.); IR: 2255, 2215 (C≡N), 1755 (sst, br.), 1525 (m); ^{1}H-NMR: 1.43 (s, 18 H), 1.39 (s, 9 H), 1.11 (s, 9 H); ^{13}C-NMR (−40 °C): 195.9 (C4), 141.9 (C6), 126.6/123.6 (C1/2), 64.8 (C7), 50.2 (C3), 47.9 (C10), 46.7 (C9), 45.7 (C8) *etc.*

Formation of adduct **4**, which has an unusual structure, *via* a radical ion-pair: It is to be expected that tetracyanoethylene (TCNE) should be capable of oxidizing **1** and **3**. However, 1:1-adducts analogous to **2** are not formed, rather unexpectedly the 1:2-adduct **4** (Table 1) instead, whose structural elucidation has involved considerable effort: on the one hand, no olefin which reacts analogously is known, and, on the other, the ^{13}C-NMR spectrum (C1 and C2 are magnetically non-equivalent) and IR spectrum appear at first sight to be inconsistent with **4**. The X-ray structure analysis, however, clears up any doubt.

Surprisingly the IR spectrum of **4** has a very intense band at 1755 and a moderately intense band at 1525 cm^{-1}. These can presumably be explained by the particular properties of the fixed structural element C4N5C6C7. C4N5C6, as a consequence of coupling, can give rise to an asymmetric and a symmetric stretching vibration, which must both be IR-active[14]. The conspicuously short wavelength absorption of the asymmetric vibration at 1755 cm^{-1} is consistent with the postulated coupling phenomenon, which at the same time shifts the symmetric stretching vibration to long wavelength (1525 cm^{-1}).

For the formation of **4** it can be assumed that the radical anion **8**, which is more bulky than **6**, attacks the radical cation **5** using a nitrogen atom as "spear point". The zwitterion **9** thus formed, in which direct ring-closure is unfavorable for geometrical reasons, finally forms the product **4** *via* ring contraction and addition of a second molecule of TCNE.

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[14] By analogy to a corresponding phenomenon in the compound $PPh_4[Cl_5Os[NC(CCl_3)NCCl(CCl_3)]]\cdot CH_2Cl_2$: R. Weber, K. Dehnicke, E. Schweda, J. Strähle, *Z. Anorg. Allg. Chem.*, in press.—We thank Prof. K. Dehnicke for his advice and assistance in interpreting the spectrum of **4**.

Semibullvalenetetracarboxylates: Models for Molecules with Bishomoaromatic Ground State**

By *Rudolf Gompper** and *Marie-Luise Schwarzensteiner*

The rate of Cope-rearrangement is drastically increased by polar substituents such as, *e.g.*, donor-acceptors[1]. In semibullvalene, which rearranges extremely rapidly, donor groups on C-1,5, acceptor groups on C-2,8 and C-4,6 or the replacement of CH by N at the 2,6 or 3,7 centers should, according to MO calculations by *Dewar*[6] and *Hoffmann*[7], increase the energy barrier of the Cope rearrangement to such an extent that a bishomoaromatic ground state results. This prediction could hitherto not be confirmed experimentally. We report here on a synthetic route which leads to semibullvalenetetracarboxylates such as **4** and **5** and should make further acceptor-substituted semibullvalenes accessible[***].

The bicyclooctane derivative **1**[13], existing as dienol **1a**, can be converted by reaction with sodium hydride and iodine into the tetramethyl 1,5-dimethyl-3,7-dioxotetracy-

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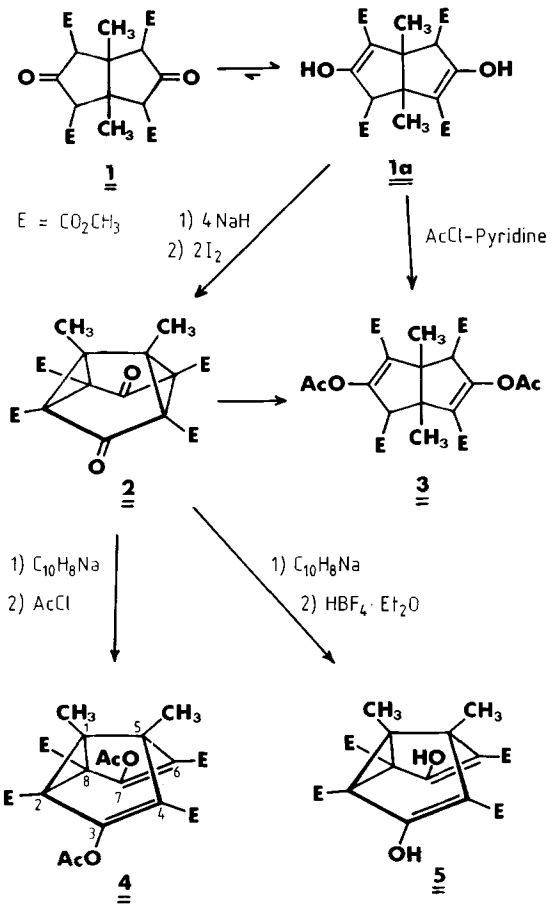
[***] *Note added in proof during publication of the short version* (February 12, 1982): In the meantime, tetramethyl 1,5-dimethyltricyclo[3.3.0.0^{2,8}]octa-3,6-diene-2,4,6,8-tetracarboxylate has also been prepared from **1** *via* **2** using another method [L. S. Miller, R. Grohmann, J. J. Dannenberg, L. Todaro, *J. Am. Chem. Soc. 103* (1981) 6249]. Like **4**, the compound does not have a delocalized structure.—The X-ray structure analysis of **4** gives C2—C8 = 1.643, C4—C6 = 2.352 Å (Dr. H. Lotter, Dr. H.-U. Wagner); in the case of **2**, C2—C8 = 1.566, C4—C6 = 1.563 Å (Dr. U. Nagel).

clo[3.3.0.0^{2,8}.0^{4,6}]octane-2,4,6,8-tetracarboxylate **2** (55%, m.p. 185 °C). Reduction of **2** with zinc/glacial acetic acid and with zinc/acetic anhydride respectively afford 1,5-dimethylbicyclo[3.3.0]octane-3,7-dione and the bisenol acetate **3** (m.p. 130 °C), which is also accessible from **1** and acetyl chloride/pyridine. Reduction of **2** with sodium dihydronaphthylide, however, and treatment of the reaction mixture with acetyl chloride, leads to tetramethyl 1,5-dimethyl-3,7-diacetoxytricyclo[3.3.0.0^{2,8}]octa-3,6-diene-2,4,6,8-tetracarboxylate **4** (25%, colorless needles, m.p. 117 °C). The IR spectrum of **4** resembles that of **3**; thus, there is little likelihood that **4** has a delocalized structure. Average ^{1}H-NMR spectra (singlets of the CO_2CH_3- and 1,5-CH_3-protons) are observed at room temperature and down to −111 °C. The ^{13}C-NMR spectra also point to a rapid Cope-rearrangement. The signal of C-2,4,6,8 first begins to broaden below −110 °C (in $CHClF_2$); at −131 °C it has almost disappeared (so far, a lower temperature could not be reached).



Hydrolysis of the mixture obtained on reaction of **2** with sodium dihydronaphthylide affords colorless crystals of the compound **5**, whose ^{1}H-NMR spectrum indicates that the dienol predominates. Remarkably, as in the ^{1}H-NMR spectrum of **4**, the 1,5-CH_3 protons yield one singlet, while the CO_2CH_3-protons give two singlets. This could be explained in terms of the OH-groups and ester groups forming chelate rings which remain intact during a rapid Cope-rearrangement.

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Tetraethyldibismuthane: A Dinuclear Bismuth Compound

By *Hans Joachim Breunig* and *Ditmar Müller**

All previous attempts[1] to prepare tetraorganodibismuthanes have met without success[**] or led at most to traces of non-analyzable products. Hence, the characterization of compounds containing a Bi—Bi bond was limited to multinuclear bismuth cluster-cations[2a] and -anions[2b] and a polymer $(PhBi)_x$[1c]. These species contain a variety of homoatomic bonds. So far, however, only one isolable compound containing a Bi—Bi bond, a chelate complex, has been described in the literature[3a]. In view of this lack of knowledge about such compounds it was surprising to find how easy tetraethyldibismuthane can be generated by a method based on a synthesis of distibanes[3b].

Reaction of triethylbismuthane with sodium in liquid ammonia led to formation of a deep-red solution of sodium diethylbismuthide, which, after destruction of the ethylsodium, reacts with 1,2-dichloroethane with decoloration to give tetraethyldibismuthane[5] [eqs. (a)—(c)]:

$$Et_3Bi + 2\,Na \rightarrow Et_2BiNa + EtNa \quad (a)$$
$$EtNa + NH_4Br \rightarrow EtH + NH_3 + NaBr \quad (b)$$
$$2\,Et_2BiNa + ClCH_2CH_2Cl \rightarrow Et_2BiBiEt_2 + C_2H_4 + 2\,NaCl \quad (c)$$

Et_4Bi_2 is a red, oily liquid at room temperature. Solutions in benzene are likewise red, those in cyclohexane yellow. On cooling, neat Et_4Bi_2 first turns dark-red, and below −30 °C it appears almost black. However, similarly to Me_4Sb_2[1a], Et_4Bi_2 also assumes a yellow color once again at −196 °C.

Et_4Bi_2 proves to be more stable than expected. Although it begins to decompose to Et_3Bi and black solids, $(EtBi)_x$, and Bi already at 0 °C, it is still detectable in such samples even after a few days. Above 40 °C, however, it decomposes completely; only Et_3Bi can be isolated after distillation at reduced pressure [eqs. (d)—(e)]:

$$Et_4Bi_2 \rightarrow Et_3Bi + 1/x\,(EtBi)_x \quad (d)$$
$$3\,Et_4Bi_2 \rightarrow 4\,Et_3Bi + 2\,Bi \quad (e)$$

Decomposition according to eq. (d) was also observed in the case of the non-isolated Ph_4Bi_2[1c].

The existence of Et_4Bi_2 is confirmed by elemental analysis and by the mass spectrum[5], which contains a prominent intense molecular ion at 25 eV. At 70 eV the successive cleavage of the ethyl groups down to the Bi_2-fragment can also be observed. Et_3Bi is formed by thermal decomposition and by fragmentation, as was analogously demonstrated in the case of a distibane[4]. The ^{1}H-NMR spec-

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[**] *Note added in proof:* In a recent communication [G. Becker, M. Rössler, *Z. Naturforsch. B37* (1982) 91] the analogous compound $(Me_3Si)_4Bi_2$ is described.

trum[5] of Et_4Bi_2, like that of Et_4Sb_2, shows an ABX_3 system due to the non-equivalence of the methylene protons.

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[3] a) O. Stelzer, E. Unger, V. Wray, *Chem. Ber. 110* (1977) 3430; b) H. A. Meinema, H. F. Martens, J. G. Noltes, *J. Organomet. Chem. 51* (1973) 223.

[4] H. J. Breunig, V. Breunig-Lyriti, *Z. Naturforsch. B34* (1979) 926.

[5] Et_3Bi (18 g, 0.06 mol) is added slowly to a stirred solution of Na (2.8 g, 0.12 mol) in liquid ammonia (200 mL). A red solution is formed, to which is first added 5.9 g (0.06 mol) of NH_4Br, and then 3 g (0.03 mol) of 1,2-dichloroethane. After removal of solvent at −20 °C, the residue is washed several times with cold pentane. After removal of the pentane at −20 °C under reduced pressure there remain 10.2 g (64%) of Et_4Bi_2. — MS (25 eV): *m/z* (rel. int.): 534 (70, M^+), 505 (30, Et_3Bi_2), 296 (100, Et_3Bi), 267 (50, Et_2Bi); (70 eV): 534 (10), 505 (12), 476 (8, Et_2Bi_2), 447 (15, $EtBi_2$), 418 (10, Bi_2), 209 (100, Bi); ^{1}H-NMR (360 MHz, C_6H_6): ABX_3-system with $-CH_3=X_3$, $-CH_2-=AB$; X_3: $\delta=2.15$ (t, J(H—C—C—H) = 8 Hz); A: $\delta=2.41$, B: $\delta=2.51$ (J(H—C—H) = 18 Hz); IR (film): $\nu(BiC_2)=450\ cm^{-1}$; UV (cyclohexane): $\lambda_{max}(\varepsilon)=225$ (25000), 290 (6060), 442 nm (84).

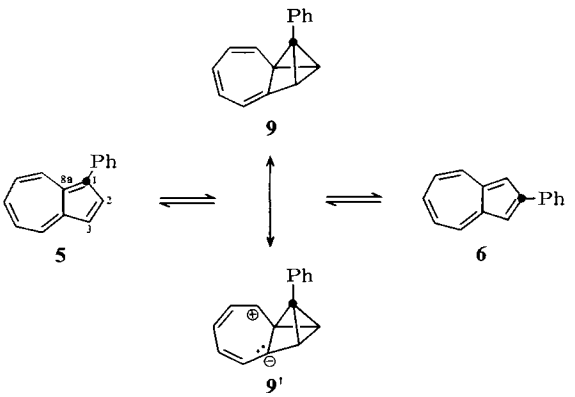
1-Phenylazulene→2-Phenylazulene Rearrangement—Substituent Migration or Skeletal Rearrangement?**

By *Klaus-Peter Zeller**

The thermal rearrangements of 1-substituted azulene derivatives into the 2-substituted isomers were previously[1] regarded as substituent migrations. After studies on the thermolysis of ^{13}C-labeled azulene[2] revealed thermal automerization of the azulene, the assumption of a skeletal rearrangement also seemed justified.

Using the reversible conversion of 1-phenylazulene into 2-phenylazulene[1] as example, we have studied the mechanism by means of a ^{13}C-labeling experiment. The 2-phenylazulene **6** formed on gas-phase thermolysis (400 °C) of 1-phenyl-[1-^{13}C]azulene **5** contains all the ^{13}C-enrichment on C2—thus, a skeletal rearrangement must take place.

From the labeling experiment and from older findings, according to which substituents on the seven-membered ring retain their position during such rearrangements[1], an interpretation of the reaction mechanism requires that 1) no changes should occur at the seven-membered ring; 2) C1 must be coupled with C3, and C2 with C8a; 3) the bonds C1—C8a and C2—C3 must be broken.



Rearrangement *via* the bicyclo[1.1.0]butane intermediate **9** fulfills these conditions. However, the postulation of **9** is at first problematic, because an *endo,endo*-bridged bicyclo[1.1.0]butane should thermally isomerize to a *cis,trans*-1,3-butadiene, irrespective of whether the reaction is regarded as a concerted $[_\sigma 2_s + _\sigma 2_a]$-mechanism or a two-step process *via* a biradicaloid intermediate[5]. Interestingly, however, thermal opening of benzvalene to benzene is premitted, since a favorable six-electron process takes place here through participation of the double bond[6]. In the case of the reaction sequence **5** ⇌ **9** ⇌ **6** it would be necessary to check whether an electron distribution as in the resonance structure **9'** with participation of a free electron pair renders possible the thermal conversion of the bicyclo[1.1.0]butane system into a *cis,cis*-1,3-butadiene structural moiety.

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[5] M. J. S. Dewar, S. Kirschner, *J. Am. Chem. Soc. 97* (1975) 2931.

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Monomolecular Membranes from Synthetic Macrotetrolides**

By *Jürgen-Hinrich Fuhrhop**, *Karin Ellermann*, *Hans Herrmann David*, and *Joachim Mathieu*

Long-chain hydrophobic molecules, in which two α,ω-sited hydrophilic heads can be introduced, are useful for the synthesis of specific monomolecular membranes with different head groups. If this "hydrophilation" proceeds in high yield, the hydrophobic educts and amphiphilic products can be separated by straightforward crystallization. We now report the first synthesis of maleic acid macrotetrolides which with sulfides and sulfites give good yields of readily isolable membrane components.

Maleic anhydride reacts with 1,12-dodecanediol to afford the dicarboxylic acid **1** (100%), which can be cyclized with a further 1,12-dodecanediol to form the 36-membered *Z,Z*-macrotetrolide **2**; isolation (40%) follows by single crystallization from ethyl acetate[4, 5]. Photochemical isomerization results in the presumed wedge-shaped *E,Z*-stereoisomer **3** (70%)[5], and the action of heat on an ethanolic solution in presence of piperidine gave the *E,E*-diastereomer[5].

Reaction of macrotetrolide **2** in isopropanol-water 4:1 with sodium hydrogen sulfite yielded the analytically pure

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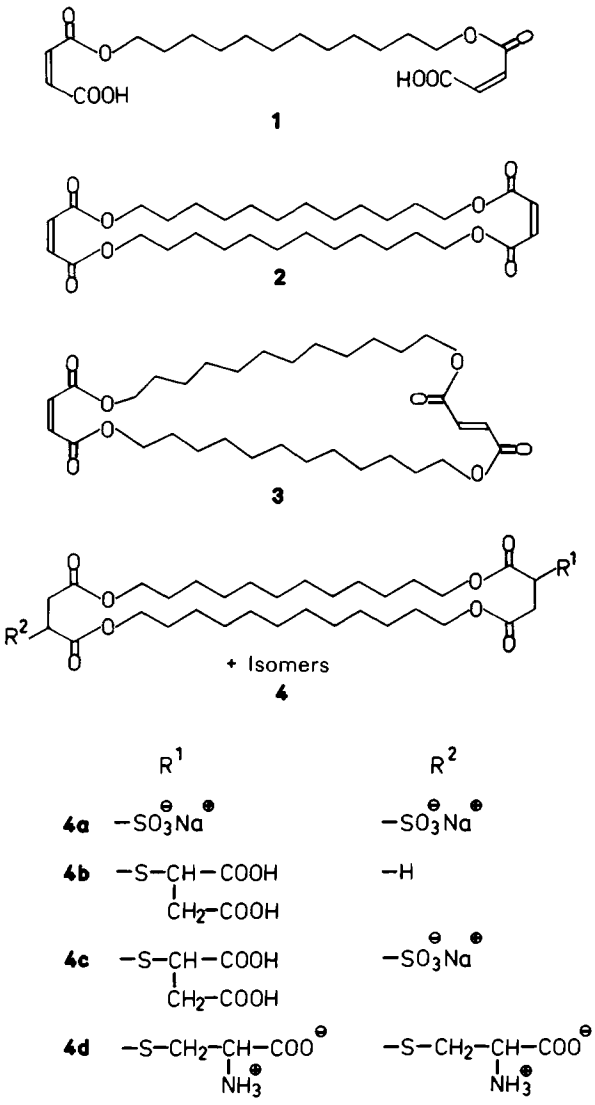
disulfonic acid **4a**[6], after crystallization from methanol-water. Addition of thiosuccinic acid to **2** led to the mono-adduct **4b**[6] (90%), which reacts with sodium hydrogen sulfite to furnish the unsymmetrically substituted macrotetrolide **4c** (80% total yield). **4d** was obtained from **2** and cystein.



4c, which is insoluble in water, yielded vesicles upon ultrasonication; with **4a**, formation of vesicles was observed after addition of cyclohexylamine and ultrasonication. Molecular models indicate that the monolayer membranes should be only 20 Å thick.

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[4] All compounds gave satisfactory elemental analyses, the expected spectroscopic data (^{1}H-NMR, IR, MS), and were homogeneous according to thin layer chromatography.

[5] Chromatographed on silica gel plates impregnated with silver nitrate. ^{1}H-NMR: *Z*-methine; $\delta = 6.24$; *E*-methine: $\delta = 6.86$.

[6] ^{1}H-NMR: **4a** (in DMSO); dd (AB) $\delta = 3.65$ for methine protons, next to $SO_3^{\ominus}$; **4b** (in $CDCl_3$ as dimethyl ester); 2 dd (AB) at $\delta = 4.09$ and 4.17 for the two methine protons next to S.

Bis(dinitrogen)- and Diethylene-molybdenum(0) Complexes**

By *Ernesto Carmona*, José M. Marín, Manuel L. Poveda, Jerry L. Atwood, Robin D. Rogers,* and *Geoffrey Wilkinson*

Although a large number of dinitrogen complexes[1] of Group 6A metals containing tertiary phosphane ligands have been isolated, for monodentate trialkylphosphanes, apparently only *cis*-$[Cr(N_2)_2(PMe_3)_4]$ is known. The complex $[MoCl_3(PMe_3)_3]$, when treated with dispersed sodium and PMe_3 in tetrahydrofuran (THF), gives *cis*-$[Mo(N_2)_2(PMe_3)_4]$ **1**, in yields better than 60%. With sodium amalgam, the corresponding *trans* isomer is formed, also in good yields. The IR spectrum of the *cis* complex (Nujol) contains two strong bands at 2010 and 1950 cm^{-1}, that of the *trans* isomer a strong band at 1930 cm^{-1} and a very weak band at 2000 cm^{-1}.

Reaction of **1** with C_2H_4 in petroleum ether (ambient temperature and pressure) affords *trans*-$[Mo(C_2H_4)_2(PMe_3)_4]$ **2** as an amber-colored, very air-sensitive crystal line substance, whose structure was determined by X-ray diffraction (Fig. 1)[5]. The ^{1}H-NMR, spectrum shows bands due to the C_2H_4- and the PMe_3-protons [$(C_6H_6)\delta = 1.4$ (s) and 1.0 (s)], respectively.

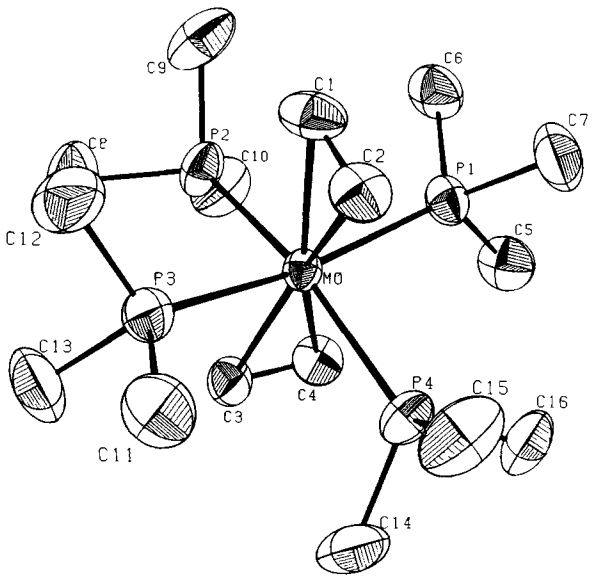

Fig. 1. ORTEP diagram of the structure of **2** in the crystal.

2 is essentially octahedral with the ethylene molecules staggered with respect to one another and eclipsing the *trans*-P—Mo—P bonds[7]. This conformational preference has been predicted from quantitative calculations[9]. The

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four phosphorus atoms lie almost in the same plane; the average MoP distance is 249.2(8) pm. Both ethylene molecules are symmetrically bound to the Mo atom, the mean distance for the C=C bonds being 140(1) pm (6 pm longer than in free ethylene).

In hydrocarbon solutions of **2**, the following equilibrium appears to exist:

$$\underset{\mathbf{2}}{[Mo(C_2H_4)_2(PMe_3)_4]} + N_2 \rightleftarrows \underset{\mathbf{3}}{[Mo(N_2)(C_2H_4)_2(PMe_3)_3]} + PMe_3$$

This was demonstrated by molecular weight determinations under He and N_2 and by IR and NMR spectra. Prolonged interaction with N_2 followed by reduction in volume in a vacuum leads to a bright yellow crystalline solid which redissolves on admission of N_2. The sequence is reversible and may be described in terms of the following equation:

$$2\underset{\mathbf{3}}{[Mo(N_2)(C_2H_4)_2(PMe_3)_3]} \underset{+N_2}{\overset{-N_2}{\rightleftharpoons}} [Mo_2(\mu\text{-}N_2)(C_2H_4)_4(PMe_3)_6]$$

That the dinitrogen in **3** is weakly bound is also indicated by the high value[11] of ν_{N_2} (2070 cm^{-1}) and by its facile displacement by CO to give colorless crystalline $[Mo(CO)(C_2H_4)_2(PMe_3)_3]$, a compound in which the C_2H_4-ligands are likewise *trans*-oriented.

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[5] **2** forms monoclinic crystals; space group $P2_1/n$, $a=10.165(3)$, $b=13.683(3)$, $c=17.139(5)$ Å, $\beta=98.84(3)$, $V=2355.5$ Å^3, $\rho_c=1.29$ g cm^{-3}, $Z=4$ and $\mu(Mo_{K\alpha})=8.1$ cm^{-1}. 2715 reflections ($I>3\sigma(I)$), $R=0.043$.
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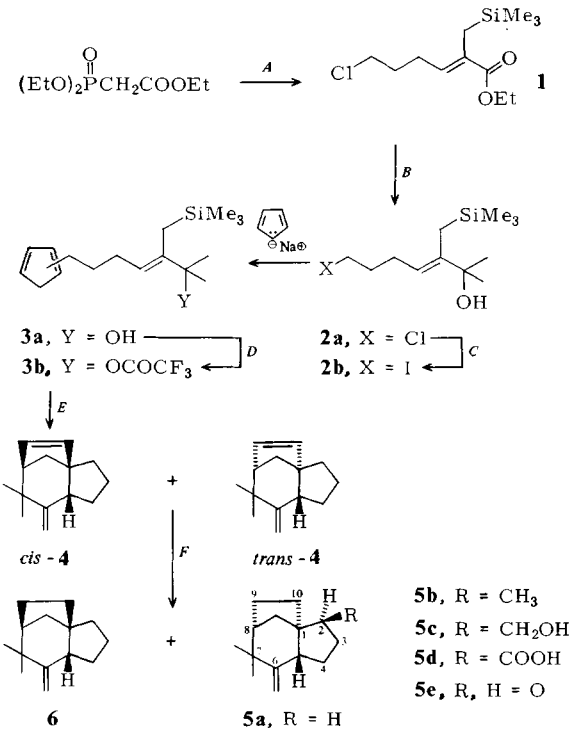
A Short Route to 7,7-Dimethyl-6-methylenetricyclo[6.2.1.0^{1,5}]undeca-9-ene and the Zizaene Class of Sesquiterpenoids**

By *H. M. R. Hoffmann, Rolf Henning*, and *Olgierd Romuald Lalko**

Zizaene **5b** and its oxygenated derivatives **5c–e** are important olfactory constituents of vetiver oil and, as has just been reported, also excellent insect repellents[1c]. Despite a number of published syntheses[1a,b], practical approaches to **5** remain a special challenge. We have now found a short route to racemic **5a**, in which the tricyclic skeleton is constructed by intramolecular cycloaddition of an allyl cation in a single step.—This work extends previous syntheses of 3-methylenebicyclo[3.2.1]oct-6-enes[2].

The functionalized acrylic ester **1** was obtained in a single flask reaction in 30% yield by (*i*) deprotonation of triethyl phosphonoacetate with sodium hydride in solvent 1,2-dimethoxyethane, (*ii*) alkylation with iodomethyl(trimethyl)silane, (*iii*) renewed deprotonation and (*iv*) Horner-Wittig reaction with 4-chlorobutyraldehyde. Methylation of **1** with an excess of methyllithium at −30 °C gave allylic alcohol **2a** (90% yield), which was converted into **2b** (Cl/I exchange 86%) by refluxing with sodium iodide in solvent acetone. Treatment of **2b** with cyclopentadienylsodium afforded the mixture of the 1- and 2-alkylated 1,3-cyclopentadienes **3a**, isolated in 87% yield by chromatography.

The key intramolecular double cyclization was carried out after developing methodology for generating highly alkylated allyl cations, which are prone to proton loss, from sensitive precursors at low temperature[3]. For example, esterification of **3a** with trifluoroacetic anhydride/ethyldiisopropylamine at −70 to −30 °C followed by chromatography of the reaction mixture at −30 °C gave the title compound **4** (*trans*-**4** : *cis*-**4** = 1.15 : 1; 16% yield with respect to **3a**) as a colorless liquid, having a fresh characteristic odor reminiscent of camphene. Addition of **4** to a concentrated solution of *ca.* 1.3 equivalents of silver nitrate in deoxygenated water gave an immediate precipitate of the silver nitrate complex, stable at −20 °C. Recovery of **4** by treatment with moist ether or pentane was quantitative. Hydrogenation of **4** with diazene occurred selectively at the endocyclic double bond, giving **6** and 2-norzizaene **5a** in quantitative yield (Scheme 1).



Scheme 1. *A*) 1. NaH in 1,2-dimethoxyethane; 2. Me_3SiCH_2I, 70 °C, 3 h; 3. NaH, 0 °C → RT; 4. $Cl(CH_2)_3CHO$, 0 °C → RT; *B*) >2 equiv. MeLi, Et_2O, −30 °C; *C*) NaI, acetone, reflux, 48 h; *D*) $(CF_3CO)_2O$, $EtN(iPr)_2$, CH_2Cl_2, −70 → −40 °C; *E*) chromatography on neutral Al_2O_3 (activity I) coated with $ZnCl_2$, CH_2Cl_2/pentane, −30 °C; *F*) N_2H_2, MeOH, RT.—NaC_5H_5 from cyclopentadiene and Na-dispersion on neutral Al_2O_3 (activity I) in tetrahydrofuran.

The new route to functionalized tricyclo[6.2.1.0^{1,5}]undeca-9-enes is short and flexible. The strained endocyclic

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bond in **4** fulfills several useful functions by (*i*) providing a site for silver nitrate complexation, thus allowing easy separation, purification and storage of oily **4**; (*ii*) introducing tricyclic strain, thus holding the labile methylene double bond in the *exo*-position, without danger of isomerization into the otherwise more stable endocyclic 5,6-position[1b,4]; (*iii*) allowing access to new analogues of zizaene which have not yet been encountered in any natural products.

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Trialkylsilyl(trifluoromethyl)diazenes as Tailored Reagents for Nucleophilic Trifluoromethylation**

By *Uwe Hartkopf* and *Armin de Meijere**

The search for novel methods of introducing trifluoromethyl groups into organic molecules continues[1]. Nucleophilic transfer of trifluoromethanide carbanion was, until quite recently, unknown[2]. We therefore designed the novel trialkylsilyl(trifluoromethyl)diazenes **2** which should be suitable candidates for the generation of $CF_3^\ominus$ ions under extremely mild conditions because of the exceptional electrophilicity of trialkylsilyl groups bound to heteroatoms.

Trialkylsilylamines proved to be inadequately nucleophilic for reaction with trifluoronitrosomethane, which converts primary alkylamines into trifluoromethylazo-compounds[1]. The lithium silylamides **1**, however, react smoothly with CF_3NO. Thus, reaction of lithium bis(trimethylsilyl)amide **1a** and of lithium *tert*-butyldimethylsilylamide **1b** with CF_3NO in diethyl ether afforded pale-red solutions of **2a** and **2b**, respectively; however, only **2b** could be enriched to a purity of up to 95% by preparative gas-chromatography (Table 1). **2a** decomposes very rapidly on attempted isolation, while **2b** is extremely sensitive to hydrolysis: Traces of moisture initiate autocatalyzed decomposition to the respective disiloxanes and silanols, trialkylsilyl fluorides, and other trialkylsilyl derivatives. Ethyl- and phenylsubstituted compounds **2** were lacking hydrolytic and/or thermal stability as well, and accordingly, could only be generated in solution and detected by combined GC/MS.

Such diazenes **2** with adequately bulky groups on the silicon, as in **2g** and **2i**, however, are completely stable. The tri-*tert*-butylsilyl derivative **2g** is a violet solid (m.p. 37–38 °C), the raspberry-red crystalline dimethyl [tris(trimethylsilyl)methyl]silyl derivative **2i** (m.p. ≈200 °C (dec)) can be heated under atmospheric conditions up to ≈200 °C without decomposition (Table 1). Accordingly, **2g** and **2i** provide a means of investigating the bonding properties of this new class of compounds.

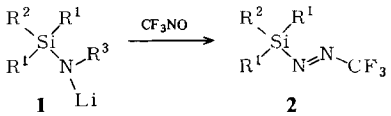
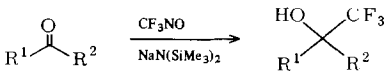


Table 1. Trialkylsilyl(trifluoromethyl)diazenes **2** from lithium silylamides **1** and trifluoronitrosomethane at −80 °C.

	R^1	R^2	R^3	Solvent	Yield [%] [a]	λ_{max} (ε_{max})
a	Me	Me	$SiMe_3$	Et_2O: Bu_2O	—	—
b	Me	*t*Bu	H	Et_2O	6	520 (6)
g	*t*Bu	*t*Bu	H	Et_2O	11	548 (24)
i	Me	$C(SiMe_3)_3$	H	Et_2O	33	504 (15)

[a] Gas-chromatographically isolated yields.

The observed sensitivity of the other compounds **2** towards hydrolysis was regarded as an indication that they fragment, as expected, with liberation of $CF_3^\ominus$ ions. Indeed, it was possible to carry out fragmentation of **2a** *in situ*, even at −100 °C, and to trap the $CF_3^\ominus$ ions thus liberated with carbonyl compounds. A solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran was added dropwise at −100 °C to a solution of CF_3NO and carbonyl compound in the same solvent. Thus, trifluoroacetophenone **4a** and cyclohexanone **4b** afforded the tertiary alcohols **5a** and **5b** (^{1}H-, ^{13}C-NMR, MS) in 34 and 30% yield, respectively (isolated gas-chromatographically).



4 5

a, R^1 = Ph, R^2 = CF_3; **b**, R^1, R^2 = $-(CH_2)_5-$

This extensible, extremely mild method complements the recently published report on a nucleophilic trifluoromethylation of carbonyl compounds[2].

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[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, Hoechst AG, and Dynamit Nobel AG.

[1] Cf. P. Gölitz, A. de Meijere, *Angew. Chem. 89* (1977) 892; *Angew. Chem. Int. Ed. Engl. 16* (1977) 854, and references cited therein.

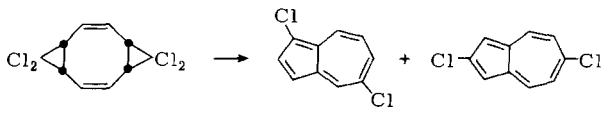
[2] According to a recent report, CF_3I reacts with zinc metal in dimethylformamide when exposed to ultrasonic sound, forming a reagent which transfers $CF_3^\ominus$ to carbonyl compounds. Cf. T. Kitazume, N. Ishikawa, *Chem. Lett. 1981*, 1679, and references cited therein.

Vacuum Pyrolysis of 5,5,10,10-Tetrachlorotricyclo[7.1.0.0^{4,6}]deca-2,7-diene: 1,5- and 2,6-Dichloroazulenes**

By *Eckehard V. Dehmlow** and *Marion Slopianka*

The dehalogenation of tetrahalotricyclo[7.1.0.0^{4,6}]decadienes with organolithium compounds leads *via meso*-1,2,4,6,7,9-cyclodecahexaene to naphthalene[1]. However, nothing has been described in the literature about the thermolysis and dehydrohalogenation of such compounds, whereas the related bicyclo[6.1.0]nonatrienes found much interest.

Cleavage of HCl takes place to a small extent on sublimation of the title compound **1** in a "poor" vacuum (250 °C/100—200 torr); on heating to 170 °C in quinoline, it undergoes polymerization. **1** behaves similarly in the presence of $NaOCH_3$ in $HOCH_3$[2].

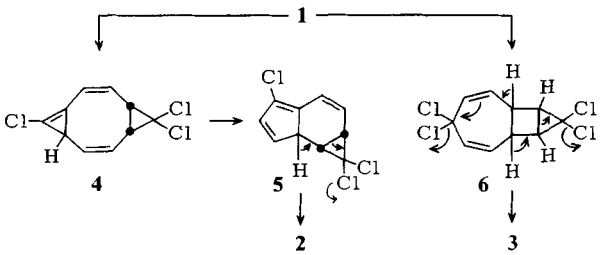


1 **2** **3**

We have now carried out a flash pyrolysis of **1** at *ca.* 700 °C/10^{-4} torr in the apparatus described by *Seybold*[3]. The blue product was free of educt. Preparative thin-layer chromatography on silica gel with petroleum ether as eluent afforded a deep-blue zone and a blue-violet zone, from which two $C_{10}H_6Cl_2$-isomers were obtained. In addition, traces of 2,6-dichloronaphthalene (but not the 1,5-isomer!) were detectable. A diffuse, deep polar-blue zone could not be obtained in a pure state.

The blue compound was shown by analysis and spectral data to be 1,5-dichloroazulene **2**[4a] the blue-violet compound to be 2,6-dichloroazulene **3**[4b].

These compounds, the first azulenes with halogen-substituents in both rings, are potentially interesting educts for further syntheses.



4 **5** **6**

For the formation of **2**, we suggest dehydrochlorination to **4**, subsequent rearrangement to **5**, and renewed dehydrochlorination. **3** can be formed *via* Cope-rearrangement to **6** and double dehydrochlorination. A reaction analogous to the intermediate formation of **6** is known in the well-investigated bicyclo[6.1.0]nonatriene series[5].

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[3] G. Seybold, *Angew. Chem. 89* (1977) 377; *Angew. Chem. Int. Ed. Engl. 16* (1977) 365.
[4] a) **2**, m.p. 89 °C; UV (ether): 772 nm (lgε = 1.99), sh 724 (2.07), 692.5 (2.39), sh 654 (2.40), 631 (2.47), sh 608 (2.41), 368 (3.76), 351 (3.73), 285 (4.60), 232.5 (4.20); ^{1}H-NMR ($DCCl_3$): δ = 8.34 (d, J = 2.2 Hz), 8.30 (d, J = 10), 7.8 (d, J = 4.2), 7.75 (dd, J = 10 + 2.2), 7.27 (d, J = 4.2), 7.05 (dd, J = 10 + 10); b) **3**, m.p. 139—140 °C; UV (ether): sh 640 nm (lgε = 2.02), 586 (2.41), 551 (2.46), 368 (3.70), 353 (3.68), 338 (3.57), 311 (3.66), 289 (4.86), sh 280 (4.80), 233.5 (4.21); ^{1}H-NMR ($DCCl_3$): δ = 8.00 (d, J = 11 Hz), 7.34 (d, J = 11) (both with further slight splitting), 7.24 (s) in the ratio 1 : 1 : 1.
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$C_\alpha C_\alpha$-Coupling of Two $\{(CO)_5CrCNEt_2\}$ Fragments by Reductive Dimerization of a Cationic Carbyne Complex[1]

By *Ernst Otto Fischer**, *Dieter Wittmann*, *Dieter Himmelreich*, and *Dietmar Neugebauer*

Addition of nucleophiles to the carbyne carbon atom of the cationic aminocarbyne complex $[(CO)_5CrCNEt_2]BF_4$ **1**[2] leads to numerous aminocarbene complexes $[(CO)_5Cr\{C(NEt_2)Nu\}]$ not usually accessible *via* conventional routes. Thus, *e.g.*, reaction of **1** with potassium diphenylarsenide affords the C_α-arsene-substituted aminocarbene complex $[(CO)_5Cr\{C(AsPh_2)NEt_2\}]$ **4**[5].

A completely different type of reaction course is observed on reaction of **1** with lithium dimethylarsenide: Instead of the expected addition of nucleophile with formation of the complex analogous to **4**, reductive $C_\alpha C_\alpha$-coupling of two $\{(CO)_5CrCNEt_2\}$ fragments takes place to give the μ-bis(aminocarbene)-complex **5** (*ca.* 30% yield, elemental analysis, MS, IR, NMR, X-ray structure analysis).

$$\underset{\mathbf{1}}{2[(CO)_5CrCNEt_2]BF_4} + 2\,LiAsMe_2 \xrightarrow[-60\,^\circ C]{Et_2O} [\{(CO)_5CrCNEt_2\}_2] + As_2Me_4 + 2\,LiBF_4$$
$$\mathbf{5}$$

The tetramethyldiarsane formed concomitantly as oxidation product can be detected mass spectrometrically in the form of the complex pentacarbonyl(tetramethyldiarsane)chromium(0). As a result of hindered rotation about the C_α—C'_α bond in **5**, two conformational isomers are formed whose existence in solution is demonstrated both by IR data as well as ^{1}H-NMR data.

An X-ray structure analysis of **5** showed that the two $\{(CO)_5CrCNEt_2\}$ fragments are crystallographically connected *via* a C_2-axis. The μ-bis(aminocarbene)-complex, however, with the longest Cr—$C_{carbene}$ bond length (219.0(7) pm)[6] found so far, shows no shortening of the C_α—C'_α (148.0(9) pm) and C_α—N (130.6(9) pm) bonds. The angle of 97.6° between the two carbene fragments Cr—C_α—N—$C_{\alpha'}$ and Cr*—$C_{\alpha'}$—N*—C_α rules out a bridging delocalized π-system[7]. Each metal atom balances its charge by a significant shortening of its bond distance to the *trans*-carbonyl group (Cr—C1 184.8(10) pm).

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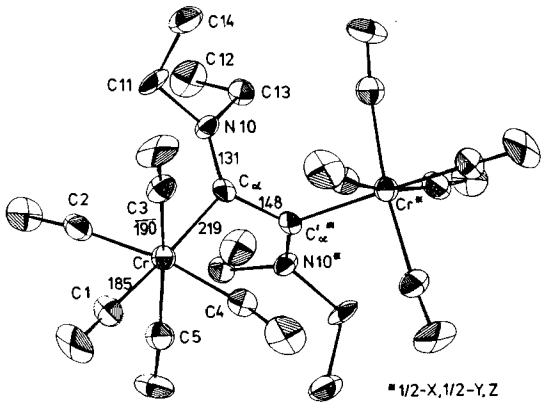

Fig. 1. Molecular structure of μ-[1,2-bis(diethylamino)ethanediylidene]-bis(pentacarbonylchromium) **5** in the crystal.

In the meantime we have also been able to demonstrate the formation of **5** in the reaction of **1** with lithium acetylacetonate; the compound is likewise formed as by-product in the aforementioned synthesis of **4**.

This novel type of reaction—reductive dimerization of a cationic carbyne complex with $C_\alpha C_\alpha$-coupling—can thus become the dominating reaction competing against addition of the nucleophile to the carbyne carbon atom when using strongly reducing nucleophiles.

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[1] Transition Metal-Carbyne Complexes, Part 70. This work was supported by the Fonds der Chemischen Industrie.—Part 69: E. O. Fischer, V. N. Postnov, F. R. Kreissl, *J. Organomet. Chem.*, in press.
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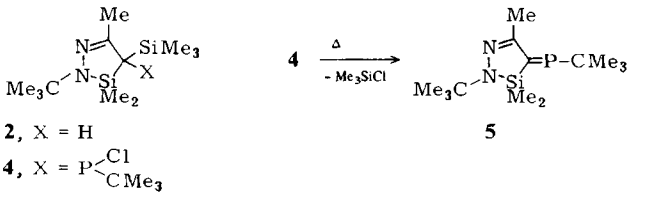
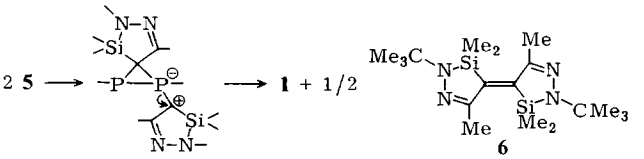
Apart from **1** only the intense red-orange compound **6** is isolated, whose structure was determined by X-ray diffraction.



We presume that by analogy with the [2+1]cycloaddition of 1,2-bis(*tert*-butyl)iminophosphane[9], two molecules of **5** react to give **1** and a carbene diazasilacyclopentenylidene, which dimerizes to **6**.



The carbene-analogous behavior of the phosphorus in **5** could result from its increased nucleophilicity produced by the *tert*-butyl group.

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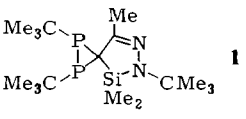
[10] **1**, yield 30%, m.p. = 116°C/0.01 torr, MS (70 eV): *m/z* 358 (35%, M^+); ^{31}P-NMR (in C_6H_6, H_3PO_4 int.): $\delta = -93.3$ (P_A), -101.5 (P_B), $J_{PP} = 206$ Hz.
[11] **6**, yield ≈15%, m.p. = 147°C, MS (70 eV): *m/z* 364 (60%, M^+); ^{1}H-NMR (in C_6H_6, TMS int.): $\delta = 0.39$ ($SiMe_2$), 1.37 (*t*BuN), 2.28 (CMe).

A Spirocyclic Diphosphirane**

By *William Clegg, Martin Haase, Michael Hesse, Uwe Klingebiel,* and *George M. Sheldrick**

Stable cyclotriphosphanes, as well as mono- and diphosphiranes[2] are known. We describe here the spirocyclic diphosphirane **1** obtained by a novel route[10].



1

In the reaction of lithiated **2** with *tert*-butyldichlorophosphane, phosphino-substituted **4** can be detected in solution. Attempts to distil **4** result in continuous loss of chlorotrimethylsilane; the expected[7,8] methylenephosphane **5** could not, however, be detected.

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Structure of the Octabismuth(2+) Cluster in Crystalline $Bi_8(AlCl_4)_2$

By *Bernt Krebs**, *Marita Hucke,* and *Claus Jörg Brendel*

Three unusual polycations of the heavy main group element bismuth—Bi_5^{3+}, Bi_8^{2+}, and Bi_9^{5+}—have so far been described in the literature[3-7], of which only the Bi_9^{5+} cluster ion has been unequivocally characterized by X-ray structure determinations on $Bi_{10}Hf_3Cl_{18}$[6] and $Bi_{24}Cl_{28}$[4]. Although solid compounds of the composition $Bi_5(AlCl_4)_3$[5,7] and $Bi_4(AlCl_4)$[5] have been isolated, preparative difficulties with respect to the synthesis of pure single crystal phases have prevented a similar structural proof of the postulated pentameric and octameric cations. The Bi_8^{2+} cluster (22 valence electrons, Bi with the very low oxidation number +0.25), whose degree of association in the chemistry of the "naked" metal cluster is still without example, seems particularly interesting. We have now been able to prepare this species in the form of pure $Bi_8(AlCl_4)_2$

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single crystals by reaction of Bi with $BiCl_3+4AlCl_3$ (33 mol-% excess of $AlCl_3$ over a "neutral" melt), and to prove unambiguously the existence and the degree of association of the cluster cation Bi_8^{2+} from an X-ray structure analysis.

The synthesis of $Bi_8(AlCl_4)_2$ was successful with a modification of the method of *Corbett*[5], however, without using $NaAlCl_4$ as a solvent. The acidities of the melts must be controlled independently of the $Bi/BiCl_3$ ratio, by changing the amount of $AlCl_3$. After subliming off the excess of $AlCl_3$, the solidified melt is deep-black and interspersed with small quantities of a second, red-brown crystalline phase.

$Bi_8(AlCl_4)_2$ forms column-shaped diamagnetic black crystals. The electronic spectrum and X-ray powder diagram are similar to those of $Bi_4(AlCl_4)$[5] and indicate both phases to be identical.

$Bi_8(AlCl_4)_2$ crystallizes hexagonally [$a=17.854(4)$, $c=12.953(3)$ Å, $\rho_{calc}=5.60\ g\cdot cm^{-3}$, $Z=6$, Laue symmetry 6/m]. The crystal structure (four-circle diffractometer, 1957 reflections, $R=0.087$) can be described in terms of space group $P6_3/m$. As an important novel structural feature the compound contains octameric Bi_8^{2+} cluster cations as shown in Figure 1 with a molecular structure of square antiprisms. The clusters are on mirror planes in the crystal and deviate only slightly from the idealized D_{4d} symmetry. The average of the observed Bi—Bi distances is 3.100 Å, which corresponds approximately to the value in metallic bismuth. The Bi—Bi—Bi bond angles in the square and triangular planes of the Bi_8^{2+} polyhedra are between 88.1(3) and 91.8(3)°, and between 59.3(3) and 60.7(3)°, respectively. Apart from two distances of 3.34(2) and 3.42(2) Å, all other intermolecular Bi...Cl distances are larger than 3.60 Å. Comparison with the Bi_9^{5+} clusters[4,6] reveals a weaker cation-anion interaction for Bi_8^{2+} (valence electron concentration of $22/8=2.75$ per Bi atom compared to $22/9=2.44$ per Bi atom in Bi_9^{5+}).

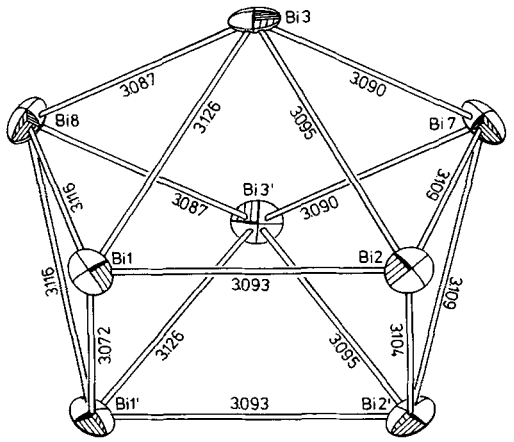

Fig. 1. Bi_8^{2+} cluster cation in crystalline $Bi_8(AlCl_4)_2$ with interatomic distances (in Å, standard deviations 0.005—0.006 Å) and vibrational ellipsoids.

The Bi_8^{2+} clusters are only incompletely shielded from each other by the relatively small anions. Remarkably short intermolecular Bi...Bi distances of 3.900(6) (Bi1...Bi3') and of 4.109(6) Å (Bi2...Bi2') seem to indicate weak inter-cluster interactions.

The structural relationship of Bi_8^{2+} to the Bi_9^{5+} cluster, which is richer by one Bi^{3+} unit, is of special interest as it may give some indication of possible paths of interconversion between the two species. The square-pyramidal Bi_8^{2+} can be transformed by very slight shifts of the atoms plus addition of one Bi^{3+} into the trigonal-prismatic tricapped Bi_9^{5+}.

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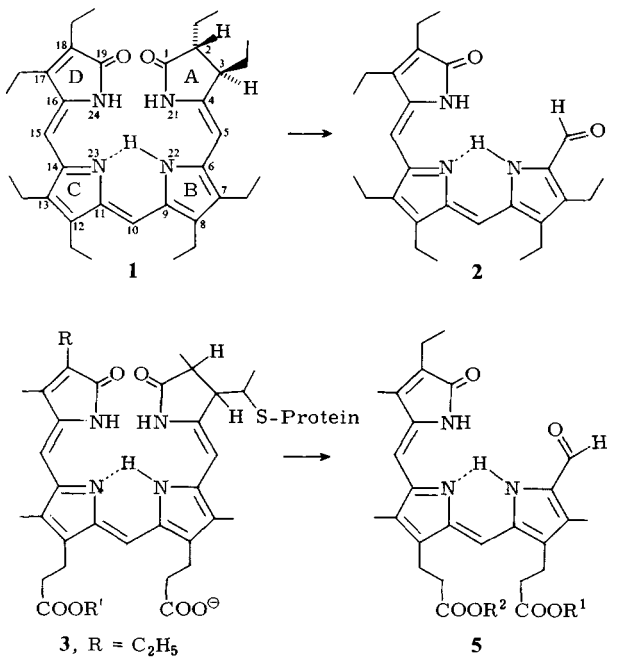
Two Mild, Regioselective Methods of Degrading Biliprotein Chromophores**

By *Werner Kufer, Corinna Krauss,* and *Hugo Scheer**

Biliproteins—receptor proteins in photosynthesis and photomorphogenesis—consist of bile pigments, which are covalently bound *via* a thioether bond at ring A to a protein; a second bond is disputed (see Discussion in [2]). We describe here two mild degradation precedures for free and protein-bound bile pigments. These methods, unlike chromic acid degradation[5], result in the retention of substantial information on the substituents at the α-pyrrolic and methine positions.



Scheme 1. (Part). **3**: R' = H or protein, **5a**: $R^1=R^2=H$; **5d**: R^1, R^2 = H, protein.

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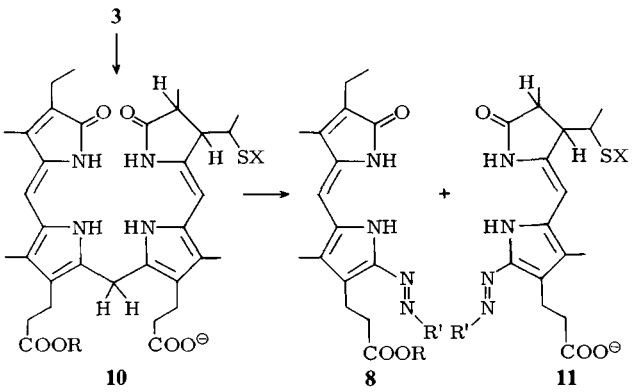
In the first method (Scheme 1), regioselective cleavage of the C-5 methine bridge occurs. Under mildly basic conditions the zinc complex of A-dihydrobilindione **1** loses the hydrogenated ring A to form **2**[6]. The biliprotein phycocyanin **3** is cleaved in an analogous manner.

3, obtained from *Spirulina platensis* (0.05 mM) was unfolded with urea (8 M). Addition of zinc acetate (0.05 mM) and titration with NaOH to pH 9.5 yielded the characteristic intermediate[6] ($\lambda_{max}=720$ nm), which afforded the zinc complex of **5a** and/or **5d** within 8 min. Using **3**, which had been degraded by trypsin, the free tripyrinone **5a** could, in addition, be isolated.

Since trypsin is not only able to cleave proteins but also ester or amide bonds to the chromophore, this result would be evidence for the existence of one of these bonds to rings B, C, or D, whereby, however, possible artifacts (partial hydrolysis, complex binding[10] *via* Zn^{++}) make an unequivocal statement difficult.



Scheme 2. (Part). R^1 = 2-ethoxycarbonylphenyl, X = protein; **8a**: R = H; **10**: R = H or protein.

In the second method (Scheme 2) regioselective cleavage between rings B and C occurs. The denatured phycocyanin **3** was reduced with $NaBH_4$ to afford the rubin **10**[13], which after gel filtration was treated with a diazonium salt *e.g.* diazotized ethyl anthranilate in 5- to 10-fold excess[11]. By means of gel filtration or extraction with organic solvents the product mixture can be separated into two fractions, of which the low molecular and less polar ($\lambda_{max}=522$ nm) is identical with authentic **8a** (rings C and D of **3**).

The high molecular and more polar fraction ($\lambda_{max}=480$ nm) should contain **11**.

A preliminary quantitative analysis of the reaction mixture indicated that approximately 14% of the extinction at 520 nm in the crude mixture disappears after extraction with organic solvents or gel filtration. Consequently, apparently at least a part of the chromophore does not contain a protein binding site at rings C or D.

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1,3-Dipolar Cycloadditions to Dialkyl-germanones and -germathiones

By *Hélène Lavayssière, Gabriel Dousse, Jacques Satgé*, Jacques Barrau*, and *Moussa Traoré*

Dialkyl-germanones $R_2Ge{=}O$ and -germathiones $R_2Ge{=}S$, novel sp^2-bonded germanium intermediates, have been characterized recently in our laboratory[1-4]. We report here new cycloaddition reactions of these unsaturated dipolar species with 1,3-dipolar reagents (nitrilimines and nitrones).

The precursor of the germanium species (see Table 1) and 2,5-diphenyltetrazole (precursor of nitrilimine) are heated in a Carius tube. Fractional distillation results in isolation of only the cycloadduct **1** (oxa- or thiadiazagermoline). **1** could also be prepared from diorganogermanium diamides and *N'*-phenylbenzo- or -thiobenzo-hydrazide.

The part structure —X—C=N— in **1** was established by IR and ^{13}C-NMR spectroscopy. The regioselectivity of these reactions is analogous to that observed with ketones and thioketones[5].

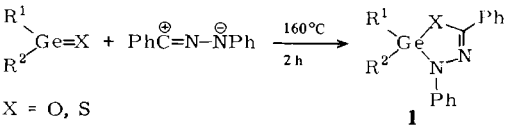
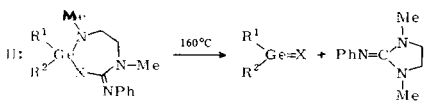


Table 1. 1,3,4,2-Oxa(or thia)diazagermolines **1**.

R_1	R_2	X	Yield [%] [a] Route I	Yield [%] [a] Route II	B.p. [°C/torr]	NMR (δ values, TMS) $GeCH_3(C_6D_6)$	NMR (δ values, TMS) —C=N—($CDCl_3$)	IR $\nu_{C=N}$ [cm^{-1}]
C_6H_5	C_6H_5	S	72	60	$250/3\times10^{-2}$	—	138.14	1535
C_6H_5	CH_3	S	70	60	$210/3\times10^{-2}$	0.77 (s)	138.7	1530
CH_3	CH_3	S	50	28	$180/4\times10^{-2}$	0.53 (s)	138.97	1528
C_6H_5	CH_3	O	—	27	$190-195/2\times10^{-2}$	0.65 (s)	152.9	1640

[a] Source of dialkyl-germanones and -germathiones.

I: $(R^1R^2GeS)_n \rightleftharpoons n[R^1R^2Ge{=}S]$;

II: 

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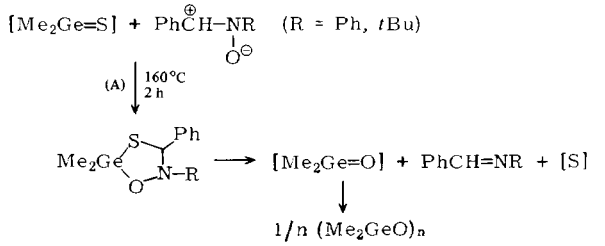
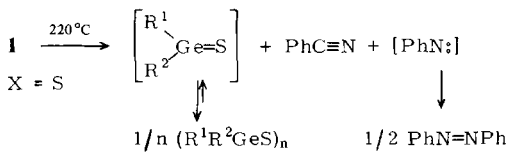
Dimethylgermathione reacts with the nitrone *N*-benzylidenephenylamine *N*-oxide at 160 °C in a Carius tube (Scheme 1, reaction A) to form an oxathiazagermolidine, which was characterized by ^{1}H-NMR spectroscopy (in C_6D_6, $\delta = 3.90$ (CH)). In the reaction with *N*-benzylidene-*tert*-butylamine *N*-oxide only thermolysis products of the cycloadduct were detected.



Scheme 1. (Selection)

An attempt to synthesize the unstable cycloadduct (R = *t*Bu) from $Me_2Ge{=}S$ and 2-*tert*-butyl-3-phenyloxaziridine (60 °C, 9 h, Et_3N) led only to the products of thermal decomposition (type 5→2+2+1). Similarly, the stable cycloadducts **1** decompose slowly above 220 °C.



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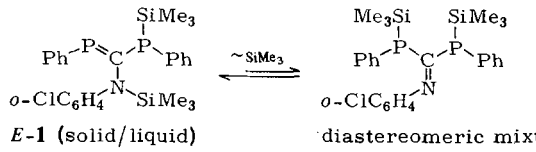
Configurational Identity (Solid, Liquid), (N→P)-Silatropism and Rotamer Detection in the Methylenephosphane $PhP{=}C(NArylSiMe_3)(PPhSiMe_3)$**

By *Rolf Appel**, *Hans Förster*, *Benno Laubach*, *Fritz Knoll*, and *Ingo Ruppert*

The transformation of *E*/*Z* stereoisomers at a specific CC-double bond during dissolution has recently been described[1]. We have now found that the spatial arrangement of the substituents at the PC double bond of methylenephosphane **1**[2] is not only stable in the crystalline state but also in solution.

According to an X-ray structure analysis the yellow crystalline *C*-amino-*C*-phosphinomethylenephosphane **1**, which can be prepared from disilylphosphane and isocyanide dichloride, has *E*-configuration[2].



E-**1** (solid/liquid) diastereomeric mixture **2**

The $^{31}P\{^1H\}$-NMR spectra recorded at room temperature in solution (AB-type, Fig. 1a–d) and on the solid substance show equal shift values for the phosphorus atoms. An *E*→*Z* isomerization during the process of dissolution can thus be ruled out.

The solution spectrum, however, contains an additional peak (Fig. 1b, c) in the shift region of the triple-bonded P-atom, which on slow cooling yields two AB patterns of different intensity (Fig. 1d–f). According to position and

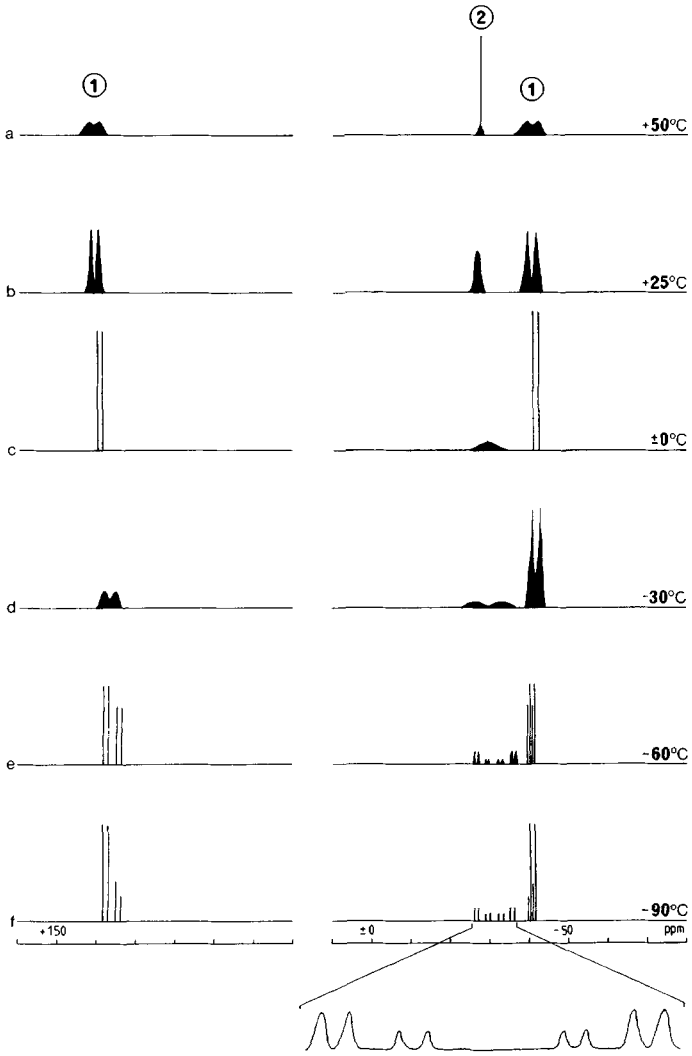


Fig. 1. $^{31}P\{^1H\}$-NMR spectra of an equilibrium mixture of **1** and **2** at various temperatures. a–f, see text.

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spectral habit they can be assigned to a 3 : 1 mixture (integration) of diastereomeric forms of the diphosphaguanidine **2** with fixed CN double bond. Formation and equilibrium behavior of the two silatautomers **1** ⇌ **2** were substantiated by the following findings.

When solid **1**, cooled to −90 °C, is dissolved in CD_2Cl_2 and measured without interruption of the cooling track at −90 °C, its isomer **2** is detectable in the $^{31}P\{^1H\}$-NMR spectrum below 0 °C, *i.e.* still no silyl migration occurs up to this temperature. The signal of **2** appears at $\delta = -23$ only above this limiting temperature. The temperature-dependent sequence of spectra is reversible. Moreover, on comparison of Figure 1a with 1b and 1c, the reverse broadening of the signals of **1** and **2** indicates the presence of a dynamic equilibrium within the NMR time scale.

In the spectrum of the methylphosphane **1** below −30 °C, an increasing differentiation of the original AB multiplet (Fig. 1e, f) can be recorded which could be due to a previously unobserved, special conformational characteristic at the methylene carbon. By comparative investigations on authentic *E*/*Z* pairs of similarly structured phosphaalkenes[2] we might possibly establish that this signal doubling is not just caused by the *Z* isomer, but by rotamers—presumably at the CN bond[3].

The silatropism is reminiscent of the equilibrium behavior of siloxy-substituted derivatives of **1**[4]; both phenomena—silatropism and hindrance to rotation—are known for (silyl)-carboxamides[5].

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Karplus Curve for $^3J(^{13}C,^1H)$ in Hydrocarbons**

By *Rafet Aydin, Jean-Pierre Loux*, and *Harald Günther**

Of the various NMR spin-spin coupling constants, particularly those between vicinal nuclei are of importance for conformational analysis, due to their torsional angle dependence postulated by *Karplus* and verified experimentally. Whereas the Karplus curve for $^3J(^1H,^1H)$[1] has been thoroughly investigated, this is not the case for $^3J(^{13}C,^1H)$[2]; specifically, until now hydrocarbons have not been studied. We therefore synthesized the deuterated norbornanes **1**–**4** and calculated the $^{13}C,^1H$ coupling constants from the measured $^{13}C,^2H$ coupling constants[3] using the well-known relationship

$$^nJ(^{13}C,^1H) = 6.5144\ ^nJ(^{13}C,^2H)$$

The $^3J(^{13}C,^1H)$ values of interest here are shown in Table 1 together with the CCCH torsion angles ϕ determined by

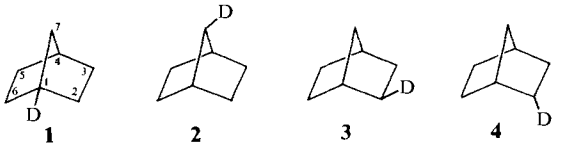

Table 1. $^3J(^{13}C,^1H)$ [Hz] in norbornane; pertinent CCCH torsion angles ϕ [°] in parentheses.

	C-2	C-3	C-4	C-5	C-6	C-7
1	—	6.76 (154)	8.75 (180)	—	—	—
2	2.21 (65)	—	—	8.54 (172)	—	—
3	—	—	1.06 (120)	—	8.78 (170)	≈0 (85)
4	—	—	2.36 (121)	—	5.28 (20)	7.08 (155)

electron diffraction measurements[4]. The dependence of $^3J(^{13}C,^1H)$ values on ϕ can be described by the function

$$^3J(^{13}C,^1H) = 3.81 - 0.90\cos\phi + 3.83\cos 2\phi \qquad (a)$$

which is displayed graphically in Figure 1. Excellent agreement with the results of calculations on propane is found[5]. Hence, bearing in mind the known reservations[1], eq. (a) can be used for the conformational analysis of hydrocarbons and serves as a basis for the study of substituent effects on $^3J(^{13}C,^1H)$.

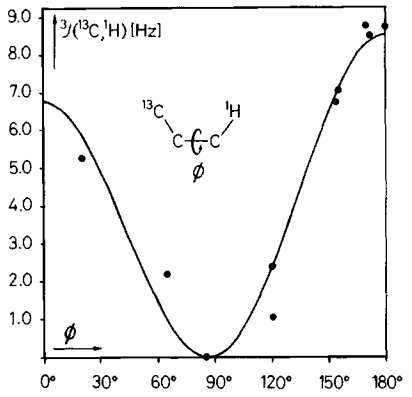

Fig. 1. Dependence of $^3J(^{13}C,^1H)$ in norbornane on the torsion angle; • experimental, — calculated from eq. (a).

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"Contra-Steric" Alkylation of the Enolates of Dioxolanecarboxylic Acid Esters

By *Wolfgang Ladner**

The deprotonation of the *trans*-substituted dioxolanes (tartrate acetonides) **1** to yield the enolates **2** has recently been described[1]. On reaction with electrophiles these enolates gave preferentially the isomers **3**. Hence, the substitution **1**→**3** corresponds stereochemically to a retention.

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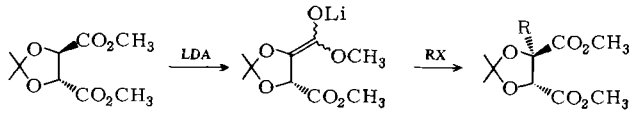
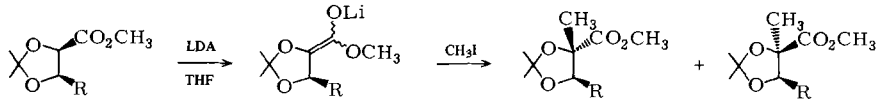


1 2 3

In the context of another investigation we generated the enolates **5** from the *cis*-substituted dioxolanes **4**. Methylation of **5** led preferentially to the isomer **6**. Hence, the conversion **4**→**6** corresponds stereochemically to an inversion. Obviously the terms inversion or retention are not relevant here, rather the enolates **2** and **5** exhibit a tendency to undergo "contra-steric"[2] alkylation *cis* to the neighboring substituents on the dioxolane ring (CO_2CH_3 in **1**[1] and R in **5**, respectively).

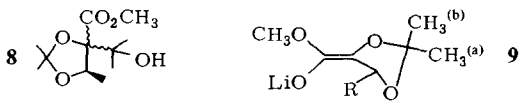


4 5 6 7

a R = CH_3–	66%	88 : 12	
b R = CH_3–CH_2–	83%	91 : 9	
c R = CH_2–$\underset{\diagdown O \diagup}{CH}$–	33%	>95 : <5	

The sterically homogeneous **4a** was obtained in 72% yield from methyl *trans*-2,3-epoxybutyrate[3] by reaction with $SnCl_4$ and acetone (molar ratio 1 : 0.2 : 1) in CCl_4 at −35 °C. After deprotonation of **4a** at −78 °C with lithium diisopropylamide (LDA) in tetrahydrofuran, methyl iodide was added (molar ratio 1 : 1.1 : 1). In the mixture of **6** and **7** obtained after warming to room temperature in all cases the diastereoisomer **6** with *cis*-orientated methyl groups (^{13}C-NMR at $\delta = 19$ ppm) predominated over the isomer **7** with *trans*-orientated methyl groups (^{13}C-NMR at $\delta = 22$–23 ppm). These structures were additionally confirmed by comparison with **7b**[4] and **7c** prepared by other routes. The stereochemical result of the alkylation should be independent of whether **4** or its *trans*-isomer is used as starting material. Thus, as expected, a sample of **4b** (ethyl ester), which contained 20% of the *trans*-isomer, afforded 90% of **6** and **7** in the same ratio 91 : 9, obtained for stereochemically homogeneous **4b** (ethyl ester).

Enolate **5a** could be hydroxyalkylated by acetone to yield **8** in 85% yield. In this case only one isomer, whose relative configuration has still to be determined, was obtained with a diastereoselectivity of >98%.



8 9

The reason for the "contra-steric" course of the alkylation is not certain. It is likely that the enolate **5** has the conformation **9** in which the methyl group (a) and the R-residues are maximally separated from each other so that the direction of alkylation is determined by the methyl group (b).

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Complexes of Crown Ethers with Uronium Salts: Preparation and Crystal Structure of [18]Crown-6 Uronium Nitrate (1/1) and Benzo[27]crown-9 Uronium Perchlorate (1/1)

By *Jos W. H. M. Uiterwijk**, *Sybolt Harkema*, *David N. Reinhoudt*, *Kari Daasvatn*, *Herman J. den Hertog Jr.*, and *Jan Geevers*

As part of our work aimed at the synthesis of molecular receptor molecules for urea we have recently described the first crystalline complex of urea with a macrocyclic polyether, *viz.* [18]crown-6 **1**[1,2].

In order to check whether the stability of urea complexes can be enhanced by protonation (at the oxygen atom[5]), we synthesized complexes of **1** with uronium nitrate (1 : 1), uronium picrate (1 : 1) and uronium *p*-toluenesulfonate (1 : 2) and a complex of benzo[27]crown-9 **2** with uronium perchlorate (1 : 1). The two title compounds were investigated by X-ray structure analysis at 168 and 269 K, respectively.

In neither of the two cases is the site of protonation affected by complexation. A very interesting feature of the structure of **1**·uronium nitrate (1/1) is the rather unusual conformation of the polyether ring ($ag^+a\ ag^-a\ ag^+g^+\ ag^+a\ ag^-a\ ag^+g^+$) which differs both from the centrosymmetric conformation of the macro-ring in the **1**·urea (1/5) complex ($ag^+a\ ag^+a\ g^+g^+a$) and from the centrosymmetric conformation of the crown in the **1**·*S-tert*-butylthiouronium perchlorate (1/2) complex ($ag^+a\ ag^-a\ ag^+a$)[11].

In the **1**·uronium nitrate (1/1) complex there are three N—H···O hydrogen bonds, namely between the uronium cation and the O(1), O(2), and O(4) oxygen atoms of the macro-ring. The guest molecule lies outside of the plane of the crown ether (Figure 1).

In the **2**·uronium perchlorate (1/1) complex the binding between host and guest is completely different from the situation described above. The cation is totally encapsulated within the crown ether with its molecular framework almost coincident with the best plane defined by the crown oxygens. The polyether ring has the conformation *asa* $ag^-g^-\ ag^+a\ ag^-a\ ag^-g^-\ ag^+a\ ag^-a\ ag^-g^-\ g^-g^-a$, where "*s*" (synperiplanar) denotes the torsion angle of almost 0°, imposed by the benzo-substituent.

All five uronium hydrogen atoms are used for hydrogen bonding to crown oxygens (Fig. 2). Although the conformation of the polyether ring is rather different from the conformation in the isoelectronic **2**·guanidinium perchlorate (1/1) complex[16] (*asa* $ag^+a\ g^-g^-g^-\ ag^-a\ ag^-g^-$

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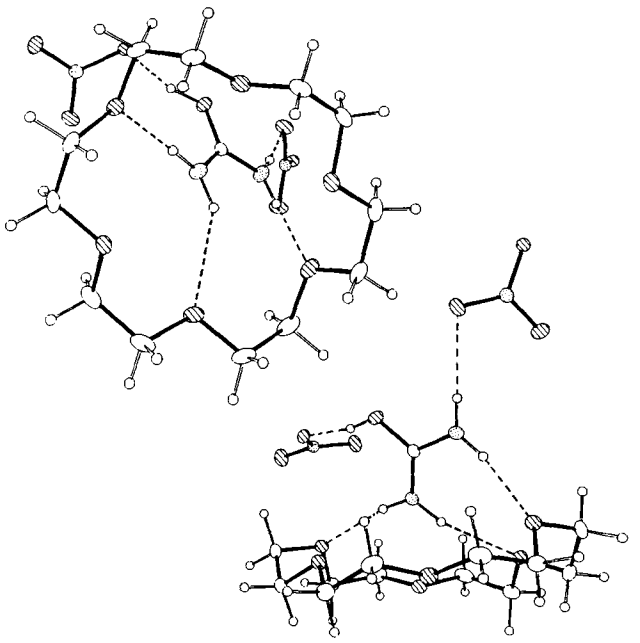

Fig. 1. Top and side views of the [18]crown-6·uronium nitrate (1/1) complex in the crystal. $P2_1/n$, $a=20.304(9)$, $b=11.604(6)$, $c=8.181(3)$ Å, $\beta=93.95(4)°$.

$ag^+a\,g^+g^+a\,ag^-a\,ag^-a$), the positions of the crown oxygens used in hydrogen bonding are quite the same relative to the central cation.

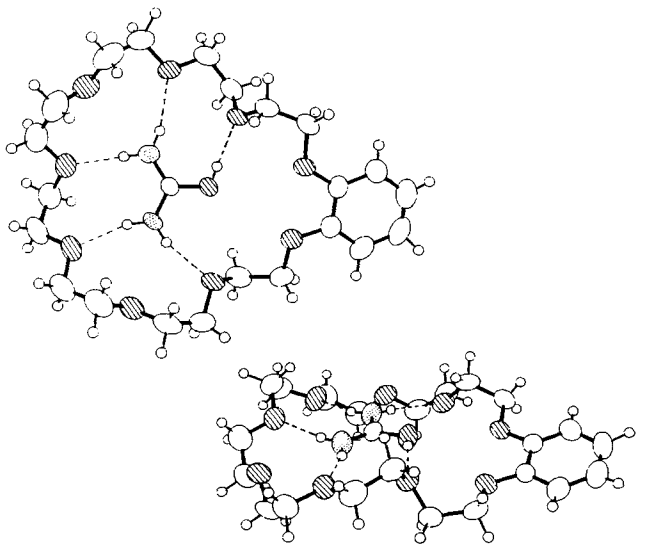

Fig. 2. Top and side views of the benzo[27]crown-9·uronium perchlorate (1/1) complex in the crystal. $P\bar{1}$, $a=13.866(5)$, $b=12.585(7)$, $c=9.926(6)$ Å, $\alpha=99.59(3)$, $\beta=74.91(6)$, $\gamma=116.52(3)°$.

The results presented here show that crown ethers in complexes with polyfunctional organic cations can assume various conformations depending upon the type of cation and anion.

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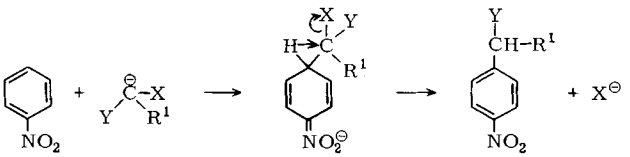
Nucleophilic Substitution of Hydrogen in Nitroarenes by Phosphorus-Stabilized Carbanions having "Vicarious" Leaving Groups

By *Mieczysław Mąkosza, Jerzy Goliński*

We have previously described the vicarious nucleophilic substitution of hydrogen in nitroarenes by carbanions containing leaving groups at the carbanionic center[1]. This principle is shown in Scheme 1.



Scheme 1. Y = stabilizing group, X = leaving group [1].

We have now found that stabilization by phosphorus-containing groups offers particular advantages. As model compounds dimethyl α-chlorobenzylphosphonate **1** and chloromethyl(diphenyl)phosphane oxide **2** were selected.

1 reacts with nitrobenzene in dimethylformamide in presence of sodium hydride to give dimethyl 4-nitrobenzhydrylphosphonate **4a** in 39% yield. In contrast, a 78% yield was obtained when the reaction was carried out in liquid ammonia in presence of powdered sodium hydroxide. For the reactions with **2**, potassium hydroxide in dimethyl sulfoxide (DMSO) was the most efficient system.

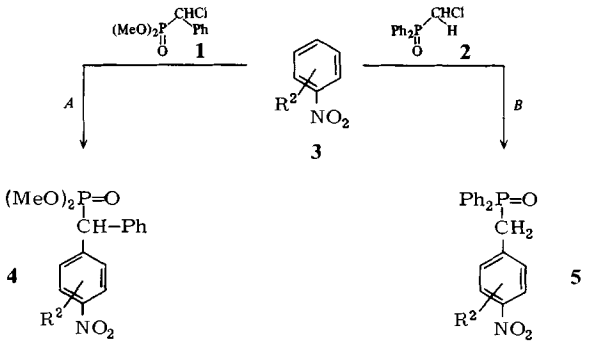


Table 1 shows examples. From these results it should be noted that the carbanions generated from **1** and **2** react with *o*- and *p*-chloronitrobenzenes *exclusively at unsubstituted positions*. No appreciable replacement of chlorine is observed, although it is strongly activated toward nucleophilic substitution by the nitro group. This is strong evi-

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Table 1. Nucleophilic substitution of hydrogen in the nitroarenes **3** with the phosphorus compounds **1** (method *A*) [3] and **2** (method *B*) [4] as precursors of carbanions [a, b].

Reagent	Product	R^2	M.p. [°C] (Solvent)	^{1}H-NMR [c] δ	J(H—P) [Hz]	Yield [%] [d]
1	**4a**	H	99.5—101 (MeOH)	4.6	26	78
1	**4b**	*o*-Cl	72—73 [e]	4.5	12	62
1	**4c**	*m*-Cl	78—79 [e]	5.1	25	65
1	**4d**	[f]	152—153.5 (EtOH)	5.4	27	31
2	**5a**	*p*-Cl	188—189.5 (EtOH)	4.2	18	41
2	**5b**	*p*-Br	195—197.5 (EtOH)	4.2	17	52

[a] Method *A*: A mixture of **1** [3] (0.01 mol) and the nitroarene (0.01 mol) in ethyl ether (15 mL) was added dropwise to a stirred suspension of powdered NaOH (4 g, 0.1 mol) in liquid NH_3 (20 ml) at −30°C. After 1 h the mixture was poured into a beaker, and after evaporation of NH_3 the residue was treated with water (100 mL), acidified, and extracted with benzene. The combined extracts were dried, the solvent evaporated, and the residue recrystallized.—Method *B*: Potassium hydroxide (4 g, 0.075 mol) was suspended in DMSO (15 mL) and to this stirred mixture (<25°C) a solution of **2** [4] (2.5 g, 0.01 mol) and **3** (0.01 mol) in DMSO (5 mL) was added dropwise. After 1 h the mixture was diluted with water (150 mL), acidified and extracted with benzene and treated further as in method A. [b] All new compounds gave correct analyses and satisfactory IR and NMR spectra. [c] In $CDCl_3$; *CH* or CH_2. [d] Not optimized. [e] Solvent benzene/hexane. [f] Educt: 1-nitronaphthalene; product: dimethyl-α-(4-nitro-1-naphthyl)benzylphosphate **4d**.

dence that the *p*- or *o*-hydrogen of nitroarenes is attacked at a much higher rate than those positions which are substituted with good leaving groups. - The process described allows the preparation of a variety of organophosphorus compounds with nitroaryl groups, which could be of significant value in organic synthesis[2].

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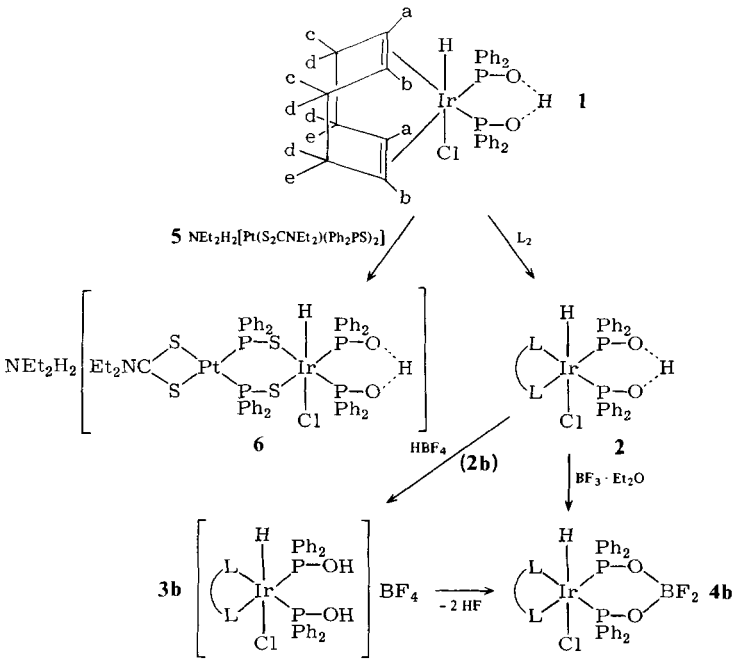
Synthesis of Novel Iridium and Rhodium Complexes Containing Diphenylphosphinito and Dimethylphosphito Ligands**

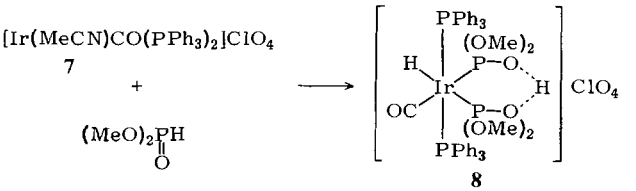
By *J. Andrew S. Duncan, David Hedden, D. Max Roundhill, T. Anthony Stephenson**, and *Malcolm D. Walkinshaw*

In recent years, a number of transition metal compounds containing the hydrogen-bonded $R_2POHOPR_2$ ligands (R = Ph, OMe, OEt) have been synthesized and some reactions of these compounds reported[1]. To date, however, the majority of these studies have been confined to complexes of palladium(II) and platinum(II). In this preliminary communication we now wish to report our attempts to synthesize related complexes of rhodium and iridium[2].

Thus, treatment of $[\{IrCl(cod)\}_2]$ (cod = cycloocta-1,5-diene) with an excess of Ph_2PCl in aqueous methanol (1:7; v/v) at ambient temperature [*i.e.* $Ph_2P(O)H + HCl$ mixture] gave as the major product, the neutral, monomeric iridium(III) complex **1**. In solution, **1** readily loses diene and therefore on treatment with bidentate ligands L_2 forms compounds **2a—c** in high yields, which show no tendency to undergo further ligand dissociation. Reaction of **2b** with HBF_4 gave the cationic complex **3b**, which readily rearranged to **4b** when redissolved in $CHCl_3$. **4b** can also be synthesized by reaction of **2b** with $BF_3 \cdot Et_2O$. Preliminary studies indicate that reaction of **1** with the platinum species **5** leads to formation of the unusual mixed metal complex **6**[4]. The synthesis of a range of such mixed metal complexes is now in progress.



a, $L_2 = Ph_2P(CH_2)_2PPh_2$; **b**, $L_2 = Ph_2As(CH_2)_2AsPh_2$; **c**, $L_2 = PhS(CH_2)_2SPh$



Similarly, treatment of the iridium complex **7** with $(MeO)_2P(O)H$ gave an almost quantitative yield of the closely related cationic complex **8**, whose configuration was determined ^{1}H-NMR spectroscopically.

In contrast, related (diene)-rhodium(I) compounds react with various $R_2P(O)H$ ligands, undergoing facile diene displacement to generate quite different species. Furthermore, the nature of the product from the reaction of $[\{RhCl(cod)\}_2]$ with an excess of Ph_2PCl in aqueous methanol depended critically on the water to methanol ratio. At low water : methanol ratios (1 : 15, v/v) the only products formed were the well-known cations $[Rh(Ph_2POMe)_4]^+$

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and $[RhH(Cl)(Ph_2POMe)_4]^+$, which were isolated as PF_6 salts[5]. However, at higher water:methanol ratios (1:7, v/v), short reaction times at ambient temperature, followed by addition of various large cations, gave high yields of the novel dinuclear, triple chloride bridged *anionic* complexes $M[Rh_2Cl_5([Ph_2PO]_2H)_2]$ ($M = AsPh_4$, $Ph_3(PhCH_2P)$, Cs). In the $AsPh_4$ salt (Fig. 1) the O...O distances of 2.4 Å are consistent with those found in other symmetrically hydrogen-bonded $R_2POHOPR_2$ complexes[1].

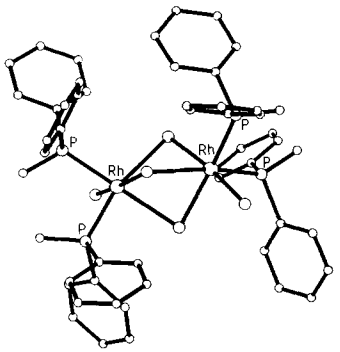

Fig. 1. Structure of the anion of $AsPh_4[Rh_2Cl_5([Ph_2PO]_2H)_2]$ in the crystal. $P\bar{1}$; $a = 12.157(4)$, $b = 16.191(5)$, $c = 20.523(8)$ Å, $\alpha = 96.02(3)$, $\beta = 99.88(2)$, $\gamma = 96.10(2)°$, $U = 3926$ Å^3, $Z = 2$. The structure has been refined to $R = 0.084$ for 4400 independent reflections ($Mo_{K\alpha}$) with $I > 2.5\sigma(I)$. Rh atoms with anisotropic temperature factors, idealized phenyl rings. Disordered CH_2Cl_2 solvent molecules not yet fully refined.

Finally, reaction of various $[Rh(diene)L_2]ClO_4$ salts with hydrogen, followed by treatment with $(MeO)_2P(O)H$ (molar ratio 1:2) led to the isolation of various air-sensitive cationic rhodium(I) complexes $[RhL_2(P(OMe)_2OH)_2]ClO_4$ ($L_2 = 2\,PPh_3$, $2\,PMePh_2$, $Ph_2P(CH_2)_2PPh_2$) in which the *tricoordinate* form of the dimethylphosphite ligand has been stabilized.

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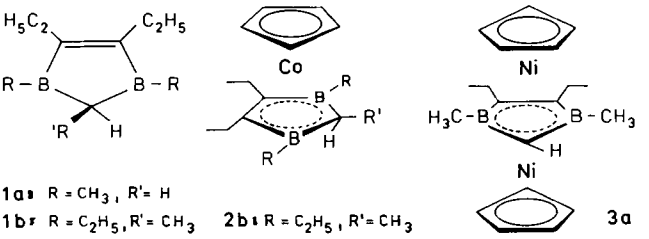
[2] For earlier studies on rhodium and iridium see: M. A. Bennett, T. R. B. Mitchell, *J. Organomet. Chem. 70* (1974) C30; H. Werner, R. Feser, *Z. Anorg. Allg. Chem. 458* (1979) 301.
[3] **1**, $^{31}P\{^1H\}$-NMR ($CDCl_3$, 301 K): $\delta = 48.2$ (s); ^1H-NMR ($CDCl_3$, 301 K): $\delta = 10.3$ (br, $Ph_2PO\mathit{H}OPPh_2$), 7.00–8.00 (m, Ph), 4.95 (br, H_a), 3.77 (br, H_b), 2.65 (m, H_d), 2.50 (d, H_c), 2.10 (d, H_e), −15.2 (t, IrH; $^2J_{PH} = 12.0$ Hz).
[4] D. M. Anderson, E. A. V. Ebsworth, T. A. Stephenson, M. D. Walkinshaw, *Angew. Chem. 93* (1981) 289; *Angew. Chem. Int. Ed. Engl. 20* (1981) 290.
[5] L. M. Haines, *Inorg. Chem. 10* (1971) 1685, 1693.

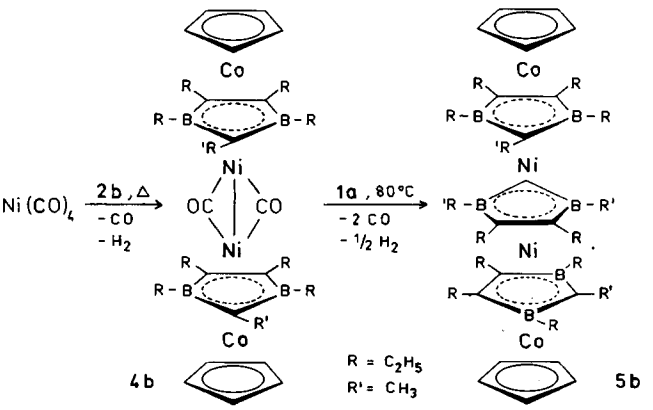
Synthesis of a Penta-decker Sandwich Complex**

By *Mark W. Whiteley, Hans Pritzkow, Ulrich Zenneck,* and *Walter Siebert**

Complexes **2**[1] with a *penta*coordinated carbon atom and an axial hydrogen atom are formed from Δ^4-1,3-diborolenes **1** and η^5-cyclopentadienylbis(ethene)cobalt. This novel type of sandwich is suitable for the synthesis of polynuclear complexes[1,2] since the formal dianion $\mathbf{1}^{2-}$ in **2** reacts with carbonylmetal complexes *via* H-elimination, in a manner analogous to the isoelectronic cyclopentadiene. We report here the directed synthesis of the CO bridged tetranuclear complex **4b** and its reaction with **1a** to afford the penta-decker complex **5b**.



Heating **2b** and tetracarbonylnickel in toluene to 80 °C results in formation of red-violet diamagnetic **4b**[3]. [$\delta^1H(C_6D_6)$: 4.07 (s, 5), 2.2 (m, 2), 2.1 (m, 2), 1.78 (s, 3), 1.5 (m, 4), 1.4 (m, 6), 1.20 (t, 6); $\delta^{11}B$: 14.8; MS (FD): *m/z* 798 (M^+, 100% rel. int.); IR: $\nu_{CO} = 1852$ cm^{-1} (in petroleum ether); yield 88%; m.p. = 256–258 °C]. **4b** has 58 valence electrons (VE) and is thus the electronic and chemical analog of $[(C_5H_5)Ni(CO)]_2$, from which **4b** can formally be prepared by inserting two 12 VE fragments of 1,3-diborolenylcobalt into the C_5H_5—Ni bonds.



Just as **1a** reacts with $[(C_5H_5)Ni(CO)]_2$ to afford the 33 VE triple-decker **3a**[4], **1a** replaces the CO bridges in **4b** to form **5b**. This first example of a penta-decker sandwich complex has 57 VE and is paramagnetic [δ^1H (D_8-THF): 30.8, 14.6, 7.7, 6.6, 5.7, 3.8, 3.1, 2.4, −3.5, −4.6, −58.9, −60.6; MS (FD): *m/z* 889 (M^+, 100% rel. int.); yield 45%; m.p. = 182–185 °C].

The unsymmetrical 30 VE triple-decker sandwich complex $[(C_5H_5)Co(\mathbf{1b}\cdot)Ni(\mathbf{1a}\cdot)]$, in which **1a**· and **1b**· signify the ligands **1a** and **1b** after elimination of H, is formed as a side product [MS(FD): *m/z* 518 (M^+, 100% rel. Int.); yield 7%; m.p. = 89–91 °C].

The constitution of **5b** is based on analytical and spectroscopic data. The ^1H-NMR spectra of **5b** and $\mathbf{5b}^{\ominus}$ (generated by reducing **5b** with potassium in [D_8]-tetrahydrofuran) and of mixtures of both species behave completely analogously to those of the triple-decker complex pairs $\mathbf{3a}/\mathbf{3a}^{\ominus}$[4]; however, in **5b** the cyclopentadienyl ligands are barely influenced by the paramagnetism. The analogy be-

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tween **3a** and **5b** is also valid for $[(C_5H_5)Ni(CO)]_2$ and **4b**.

The X-ray structural analysis [crystal data of **5b**: space group $P2_1/c$, $a = 18.411(3)$, $b = 14.411(2)$, $c = 18.860(2)$ Å, $\beta = 116.93(9)°$, $V = 4461.3$ Å^3, $Z = 4$; 4553 reflexions ($I \geq 2\sigma_I$), Syntex R3 ($Mo_{K\alpha}$ irradiation, θ-scan), $R = 0.052$ (without H atoms, anisotropic temperature factors)] confirms the penta-decker structure. Two neighboring 1,3-diborolenyl ligands are, as in analogous tetra-deckers[2], mutually *trans*-orientated, whereas the third ligand is rotated by approximately 70°. The distances of the best ring-planes to the metal centers are 1.69, 1.69 [(C_5H_5)—Co], 1.61, 1.63 [(C_2B_2C)—Co], 1.73, 1.73, 1.75, 1.73 [(C_2B_2C)—Ni]; Ni···Ni 3.48 Å.

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[1] W. Siebert, J. Edwin, H. Pritzkow, *Angew. Chem. 94* (1982) 147; *Angew. Chem. Int. Ed. Engl. 21* (1982) 148.
[2] W. Siebert, J. Edwin, H. Wadepohl, H. Pritzkow, *Angew. Chem. 94* (1982) 148; *Angew. Chem. Int. Ed. Engl. 21* (1982) 149.
[3] First obtained in trace amounts from $(C_5H_5)Co(\mathbf{1b}^{\bullet})Ni(C_5H_5)$ [4] ($\mathbf{1b}^{\bullet} \triangleq \mathbf{1b}$ after H-elimination) and $Fe_2(CO)_9$ (mesitylene, 150°C): J. Edwin, W. Siebert, unpublished results.
[4] W. Siebert, *Adv. Organomet. Chem. 18* (1980) 301; F. H. Köhler, U. Zenneck, J. Edwin, W. Siebert, *J. Organomet. Chem. 208* (1981) 137.

BOOK REVIEWS

The Inorganic Chemistry of Biological Processes. By *M. N. Hughes*. John Wiley & Sons, Chichester 1981. 2nd edition, ix, 338 pp., paperback, £ 9.90.

Although this monograph, now appearing in its second edition, was first published in 1972, in spite of the wealth of new material its size has increased by only 10% as a result of judicious pruning. The paperback edition is thus still within the reach of advanced students.

After a short and useful physiological-chemical introduction (Chapter 1) and a discussion of the properties of transition-metal ions (Chapter 2), the following main themes are treated in eleven chapters: Chapter 3—physicochemical characterization of metalloproteins and other metal-containing biologically active molecules; Chapter 4—metalloenzymes in hydrolysis and group-transfer reactions; Chapter 5—transition metals in biological redox reactions; Chapter 6—the fixation of nitrogen and the nitrogen cycle in nature; Chapter 7—oxygen transport; Chapter 8—transport and storage of iron; Chapter 9—alkali metals and alkaline earth metals in physiological-chemical processes; Chapter 10—metal ions and chelating agents in medicine; and Chapter 11—nonmetals as trace elements in the animal and plant world. More than 700 literature references, some as late as 1980, provide an up to date extension of the text.

The breadth of the material deserves a somewhat more detailed list of contents and a larger index. Thus, under "nucleic acids" one is referred to DNA and RNA, but these are not listed. In the text, the metal complexes of adenosine triphosphate and nucleic acids are treated somewhat too briefly (Chapters 1 and 9), though it must be admitted that this area of inorganic biochemistry is still very complicated. The other chapters—almost in the nature of review articles—give good introductions to the above-mentioned special fields. There are occasional false notes in the interpretation of special results, but they are not very important (p. 147: cytochromes are not hematins; p. 149: an increase in the length of the Fe—S bond in the oxidation of cytochrome c is by no means expected; p. 233: indeed, simple hemes with coordination number 5 may be prepared).

In a later (desirable!) new edition there should be illustrations of whole macromolecules that have meanwhile become known through X-ray structure analysis (*e.g.* hemoglobin, cytochrome c, carboxypeptidase, and yeast-phenylalanine transfer-ribonucleic acid) and their discussion from the point of view of inorganic chemistry, since only an attempt at a complete overview of this kind can broaden the understanding of the problems of inorganic biochemistry. Some details of the coordination chemistry and organometallic chemistry in Chapters 2 and 6 could be left out to make room.

The book, otherwise written with great sensitivity, is highly recommended to advanced students. Every chemical library should have a copy.

Johann W. Buchler [NB 565 IE]

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The Resist Technique— A Chemical Contribution to Electronics

By Hartmut Steppan, Gerhard Buhr, and Hansjörg Vollmann*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

Besides its technical meaning, the word "electronics" signifies another industrial revolution. The driving force behind this development is the very rapid progress in the field of integrated semiconductor circuits. An ever-increasing number of structures of ever-decreasing size must be accommodated on the same surface of the semiconductor crystal. This trend towards miniaturization embraces not only the integrated circuit but also its mounting panel, the printed circuit board; integrated circuits with 65536 storage spaces, *i.e.* more than 100000 individual functions, on a semiconductor die of less than 1 cm^2 are already standard today in industry. This micro-world, the potential of which can hardly be fully appreciated even today, has a direct appeal to all those of scientific inclination. However, the role of chemistry in the creation of this world becomes clear only on closer examination of the manufacturing processes: no mechanical tool is fine enough and no machine is sufficiently precise and rapid to work out complicated structures in the micron range with the required perfection. Chemistry first made possible the mass production of electronic components and consequently their widespread use today, and it is chemistry which will also play a decisive role in the future. Whether in the field of photoresists for the production of printed circuit boards with conductor widths of less than 100 μm, or in overcoming the 1 μm barrier in the manufacture of semiconductors using electron beam- and X-ray-resists, photochemistry, radiation chemistry, and polymer chemistry will have to develop new manufacturing processes and provide industrially utilizable materials.

1. Introduction

On April 14, 1981 a young man is sitting in his room in Frankfurt am Main; he presses a button, and in the next instant a runway in California appears in true-to-life colors on the screen of his television set. In the clear sky a small point appears, becomes larger, and in a few minutes the observer witnesses the space shuttle "Columbia" returning from its first space flight, gliding-in majestically and precisely, touching down on the runway, and taxiing to a standstill as though nothing in the world were more normal. The young man in Frankfurt sees the touch-down of the space shuttle at the very moment at which the landing actually takes place in California, although the runway is about nine thousand kilometers away from him. The information reaches him *via* a communications satellite "parked" in space, over the Atlantic.

What is astonishing here is the detailed functioning of a technology which today is termed electronics in the widest sense. For many of us today, electronics is a magic word which is regarded both as a promise and as a threat.

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We come into contact with applied electronics to an increasing extent in many areas of life, for example in toys, in watches, in the automobile, in calculators, in computers, in the area of television and radio, or in the heart pacemaker. Thus, not only communications technology, but also control and regulation technology are predominantly affected.

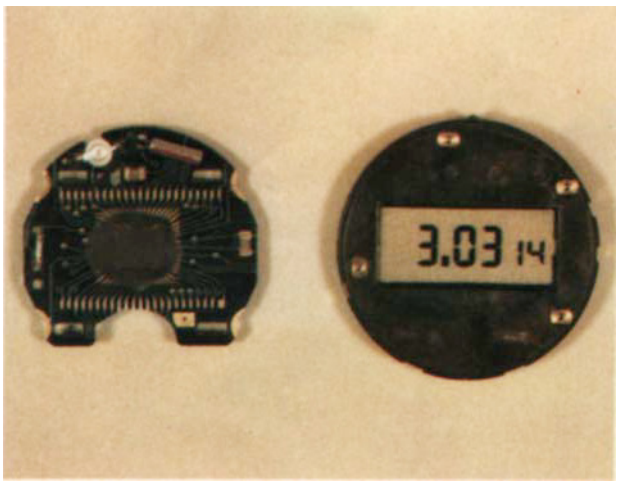


Fig. 1. View of the interior of a digital quartz watch. Left: Integrated circuit (chip coated with plastic) and other components mounted on a printed circuit board which also carries the contacts for the display. Right: Digital liquid crystal display (LCD).

Examination of the interior of a quartz watch (Fig. 1) shows the few, but important, components of this electronic device.

The actual core, the integrated circuit, is a small silicon platelet (chip), into whose surface of *ca.* 5×5 mm a large number of transistors, diodes, resistors, capacitors and other electronic functions are incorporated.

The integrated circuit also carries an extensive network of conductors, which connect the individual elements on the chip, and end in small contact points. Thin metal wires connect these points in turn with contacts on the small printed circuit board, which forms the contact with the remaining components.

The printed circuit board thus has a double function: on the one hand it is the base *i.e.* the mounting panel for the components, and on the other it contains the circuits between these components.

In this article, a closer examination will be made only of the so-called phototechniques and the chemistry on which they are based; techniques which first made possible the modern processes for the manufacture of integrated circuits and of printed circuit boards.

The discovery of the transistor effect in 1947 by *Bardeen, Barttain,* and *Shockley* was the prerequisite of our present microelectronics. In the meantime, the transistor has practically completely replaced the valve.

The second milestone in the technical development of electronic components was the introduction of the monolithic integrated circuit ten years later by *Kilby* and *Noyce*; the associated manufacturing process, planar technology, introduced the age of microelectronics.

2. Manufacturing Techniques

2.1. General

Chemistry plays a key role both in the mass production of semiconductors containing integrated components and in the production of printed circuit boards.

In this article resist is to be understood as a material which, when applied to a substrate surface, masks that part of the surface it covers *i.e.* protects it from attack by any agents, for example etching media, chemical or electrochemical metallization baths. The *resist* must therefore be *resistant* to the agents in question.

Using the resist technique, the whole component, a part of whose surface is protected by a resist layer, may be subjected to the undifferentiated action of the processing media, a technique which is indispensable for mass production.

Resist techniques have been known for some time in other areas, *e.g.* the production of letterpress and gravure printing forms by chemigraphic etching processes may be mentioned.

2.2. Masking Techniques

Resist masks having relatively coarse detailed structures (in general > 0.3 mm) can be printed onto the surface to be masked, either using the screen-printing process (Fig. 2) or magnetographically (Fig. 3).

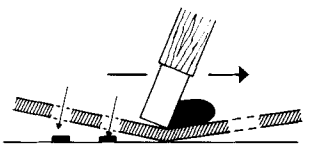


Fig. 2. Application of a resist mask by screen printing. The resists used are viscous solutions or pastes which exhibit the required resistance after printing (and drying, if they contain solvent), or achieve this resistance by subsequent crosslinking [1].

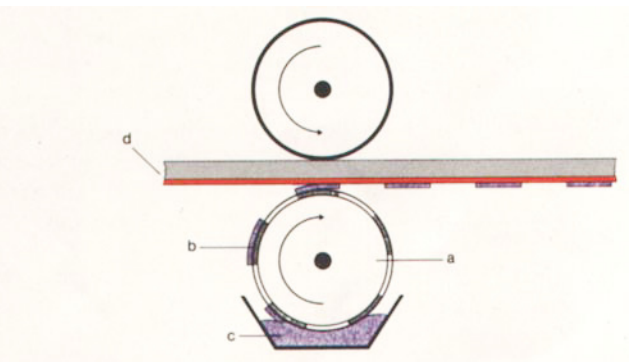


Fig. 3. Application of a resist mask by magnetographic printing [2]. The printing drum (a) has a magnetic printing form (b)clamped around it and this selectively takes up, in its magnetic areas, a pulverized magnetic resist material (c), and transfers this to the substrate (d). The powder image is then coalesced by thermal shock to give a pore-free resist layer.

Resist masks having finer structural elements are produced in most cases by the so-called photoprinting process, using photoresists (Fig. 4).

By analogy to screen printing, the term photoprinting is commonly used to describe the masking of surfaces by photoresists, although this is not a printing process.

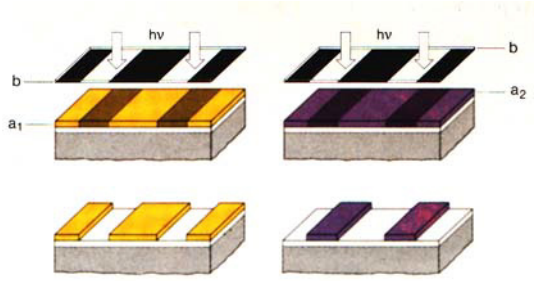


Fig. 4. Application of a resist mask by photoprinting. The total substrate surface is first completely coated with a positive (a_1) or negative photoresist (a_2). A radiation mask (b) carrying an image of the structures to be transferred in the form of areas which are permeable or impermeable to radiation, is superimposed on the photoresist layers. The irradiation changes the solubility of the resist layer under the transparent zones of the mask. After the mask has been removed, the substrate is treated with a liquid, the developer, which selectively removes the more soluble areas of the resist layer baring the substrate surface there and making it accessible to further selective treatment. The unprotected substrate areas correspond to the transparent regions of the irradiation mask of positive photoresists (a_1), and to the masked structures that are impermeable to radiation for negative photoresists (a_2).

Photoresists[3,4], in general, are understood as radiation-sensitive, in particular, photosensitive materials which undergo a change in their solubility when irradiated. According to whether the solubility is increased or decreased when irradiated, the material is termed a "positive" or "negative" photoresist, respectively. As described in more detail in Section 3, photochemical or radiochemical reactions are exploited to create a decrease or an increase in the molecular weight (polymerization or crosslinking with formation of a three-dimensional network), or cause a change in the polarity or the molecular interactions of the resist constituents.

The photoresist layer is principally applied by two processes: Either by applying a solution of the radiation-sensitive material to the surface, followed by a drying step in which the solvent is evaporated—this process is used particularly for applying thin layers—or so-called dry film resists[3g,h,5,6] are used. A dry film resist consists of a support film and a thermoplastic photosensitive layer, which in turn is covered by a protective film.

Dry film resists are commercially available as rolls. For coating, the protective film of the resist assembly is peeled off and the laminate comprising an active layer and a temporary support film is applied, under the action of heat and pressure, to the surface to be coated. Simultaneous lamination on both sides is also a technique much used today. The active layer of dry film resists is relatively thick, in general between 25 and 50 μm, but can also be up to 100 μm. The thick dry film resist layers open up a number of interesting possibilities which will be considered in more detail under the individual manufacturing processes.

2.3. Manufacture of Integrated Circuits

Today, very highly integrated circuits already contain up to 100000 or more individual components, such as transistors, diodes, resistors, capacitors, *etc.* on a semiconductor die of less than 1 cm^2 area, the chip: it essentially consists of monocrystalline silicon, the most frequently used semiconductor material.

Starting from silicon disks, the so-called wafers—those used industrially have a diameter of up to 12.5 cm—hundreds of integrated circuits are produced simultaneously in a multistage process. Depending on the process and on the type of circuit, between five and, in some cases, more than ten different resist masking steps must be used. The wafers are cut out of single crystals of silicon[7].

2.3.1. Monocrystalline Silicon

Impure silicon is produced from sand by reduction with charcoal in an electric arc furnace. The resulting material, whose principal impurity is iron, is converted into trichlorosilane, which is then purified by multistage distillation. The pure trichlorosilane decomposes on silicon rods at temperatures of $>1000\,^{\circ}C$ in the presence of hydrogen to give pure polycrystalline silicon. This is then melted in a quartz crucible, a seed crystal of the desired crystal orientation immersed in the melt, and the crystal rotated and slowly withdrawn upwards (temperature program). In this procedure, the silicon solidifies in monocrystalline form, in the predetermined orientation of the seed crystal. As a rule, before the single crystal is drawn the ultra-pure silicon is doped with impurity atoms which impart certain conducting characteristics to the single crystal (Fig. 5).

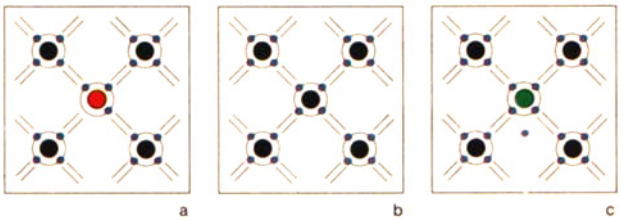


Fig. 5. Schematic details of the crystal lattice of a *p*-doped (a), undoped (b), and *n*-doped silicon crystal (c). The incorporation of atoms which, like boron, have one valence electron less than silicon produces holes, and these are filled by electrons of the neighboring atoms during the conduction process. A doped silicon crystal of this type is *p*-conducting (hole current). Incorporation of atoms with one valence electron more than silicon, for example phosphorus atoms makes the silicon *n*-conducting, electrons as charge carriers transporting the current.

The silicon single crystals are then divided into disks using special diamond saws; the disks are ground and finally polished to produce wafers.

2.3.2. The Planar Technique[3b,c,e,i,4b–d,8]

The manufacture of an integrated circuit containing a large number of individual elements begins with the design produced by the electronics engineer, generally with the aid of a computer (CAD = *C*omputer *A*ided *D*esign). Since every integrated circuit contains a large number of structures juxtaposed together, some inside others and some on top of others, and these are built up consecutively (Fig. 6), a particular radiation mask is required for each of the required photolithographic structuring steps (Fig. 7).

The production of the radiation masks, which consist of layers of silver halide emulsion on special glasses, will not be described here in more detail. However, it may be emphasized that photoresist techniques are employed for the manufacture of non-emulsion masks (chromium, chromium oxide, and iron oxide masks on glass or quartz, "hard-surface masks")[9] used in the manufacture of highly integrated circuits.

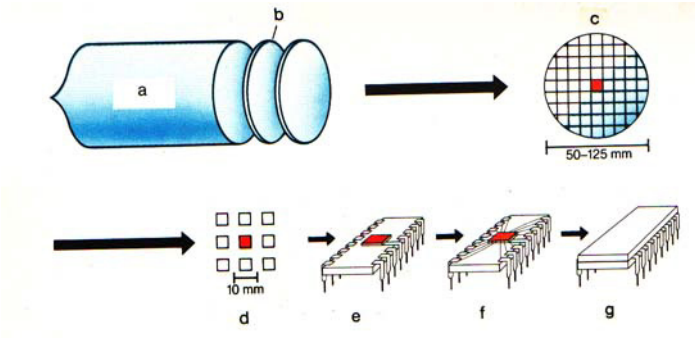


Fig. 6. Production of integrated circuits (schematic). a) Single crystal of silicon, b) wafer, c) integrated circuits (ICS) on the wafer, d) individual ICS or chips, e) chips mounted on supports, f) bonded, and g) encapsulated.

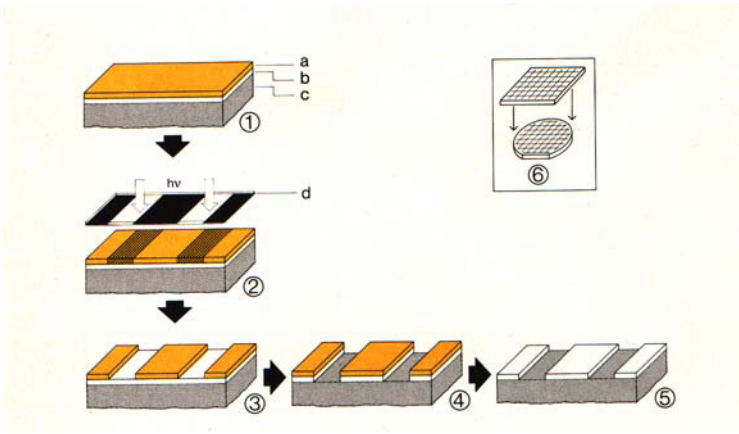


Fig. 7. Photolithography using a positive liquid resist. ① A substrate (c) is provided with an intermediate layer (b) and coated with a positive resist layer (a). ② Exposed under a photomask (d). ③ Areas of the resist layer which are exposed to light become detached in the subsequent development process. ④ In these non-protected zones, the intermediate layer is etched away. ⑤ After removing (stripping) the photoresist, the substrate is only partially covered by the intermediate layer; "windows" have been opened which made the substrate accessible to further treatment at these sites. The substrate can, for example, be the wafer and the intermediate layer silicon dioxide. However, metallic circuit paths and contacts are also produced from a metallic intermediate layer using this technique. ⑥ Represents the total photolithographic process from the application to the removal of the photoresist (see Fig. 8).

To transfer the information contained on the radiation mask, the latter is placed directly on the photoresist layer (contact exposure), or is held at a small precisely defined distance above the surface of the wafer (proximity exposure); alternatively, exposure is effected by projection using lenses or mirrors[10]. All these processes use radiation masks which contain the total information to be transferred to one manufactured plane, for all integrated circuits on the waver.

The most modern exposure method, step and repeat exposure, is used particularly for wafers of large surface area. Here, the information for each individual chip area, or for small groups of areas of this type are successively projected onto the wafer coated with the photoresist. This very precise but, compared to the area or scanning exposure processes, time-consuming method achieves an accuracy that represents the limits possible by photooptical methods.

The production of a simple transistor by the planar technique, using photolithographic processes, may be illustrated by the production of a *p*-MOSFET (*M*etal *O*xide *S*emiconductor *F*ield *E*ffect *T*ransistor, see ⑨, Fig. 8). A tiny section (25×25 μm) of an integrated circuit is shown in Figure 8.

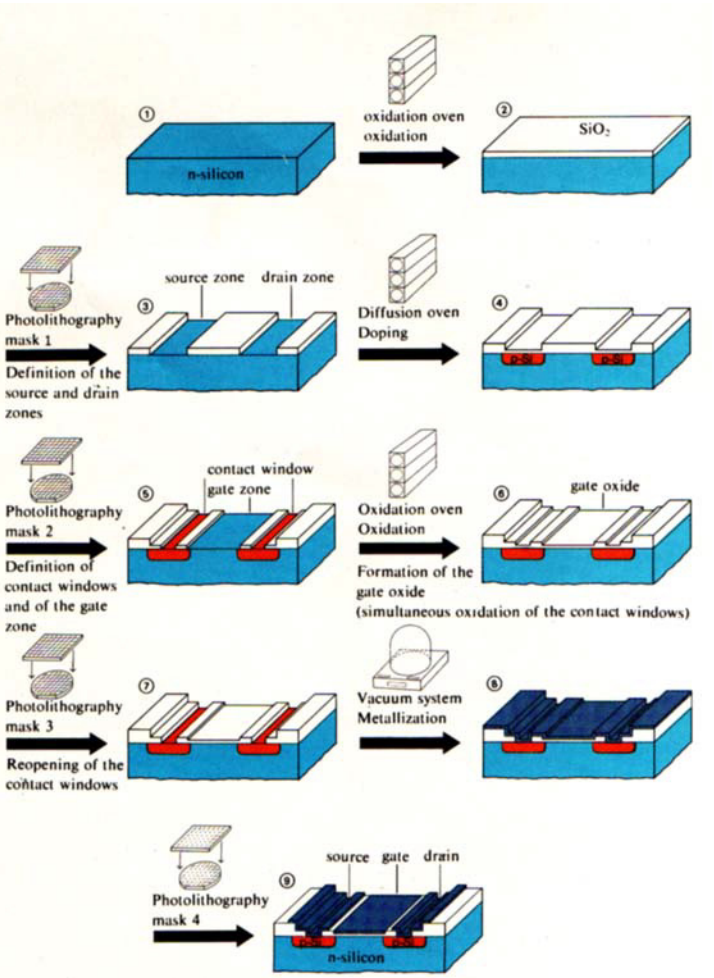


Fig. 8. Planar technology: Manufacturing scheme for an individual MOSFET in 9 stages. In ⑨, a negative voltage applied across the gate controls the current flow between source and drain. For further details see text.

The base material for the *p*-MOSFET is an *n*-doped wafer ①. A thin silicon dioxide layer ② is first grown on this wafer in an oxidation oven. This is followed by the photolithographic step 1 (see Fig. 7), which defines the source and drain zones ③ *i.e.* the silicon surface is exposed in these areas, and subsequent doping takes place only at these sites. All other areas are protected by the silicon dioxide mask manufactured by photolithography.

If atoms carrying only three valence electrons are allowed to diffuse into the source and drain zones, these zones become *p*-doped. The process is terminated by slight oxidation of the *p*-doped areas ④.

In the photolithographic step 2, the contact windows in source and drain are opened, and the gate zone is formed ⑤. Another oxidation step produces a thin, well-defined silicon dioxide layer, the so-called gate oxide ⑥. Since the contact windows in the source and drain areas have again been closed in this step, they must be opened again in photolithographic step 3 ⑦.

After metallization ⑧ in photolithographic step 4, the metal contacts for source, drain, and gate are established ⑨.

The entire integrated circuit is further coated with a passivating layer in whose edges windows are opened *via* a

further photolithographic step. This later enables the circuit to be contacted and connected with the appropriate pins used to plug it into the printed circuit board and for subsequent soldering steps (see Fig. 6).

To produce structures of this type on the μm scale, the highest requirements are made on the quality of the processing tools, on the consistency of the photoresist, and on the reproducibility of the total processing method[11].

2.3.3. Future Developments

The smallest windows which are currently opened by the photolithographic process in the mass production of integrated circuits are 2 to 5 μm in diameter (Fig. 9)[12]. The last decade has seen a progressive miniaturization of the structures down to these dimensions. By 1985, a further reduction in the diameter of the smallest reproduced structures to between 1 and 2 μm is expected[12]. Structures in the submicron scale have already been realized in the labo-

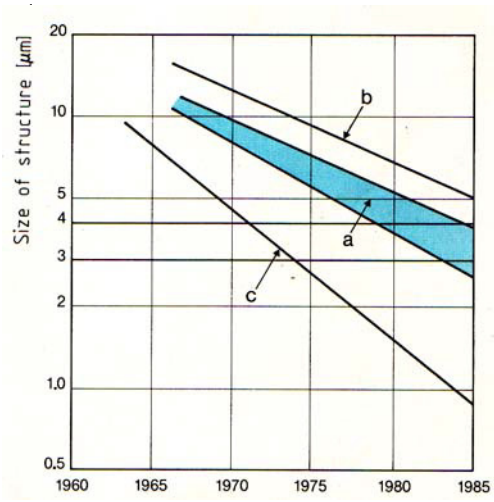


Fig. 9. Sizes of structures, development in the years 1960—1985. a) Range of structural dimensions which can be mass produced; b) sizes of structures in components with low resolution requirements, and c) limits achievable by demanding manufacturing techniques.

In order to make progress with photolithographic processes in these dimensions, a basic restriction has to be overcome. Currently, high pressure mercury lamps, which have an intense emission between 366 and 436 nm, are predominantly used in photolithography. Structures whose dimensions are smaller than these wavelengths cannot be reproduced by photooptical processes. To overcome this limit, light of shorter wavelength must be used for the imaging process *e.g.* short wavelength UV light, so called "deep UV" ($\lambda = 200-300$ nm)[13, 14b]. More far-reaching possibilities are offered by electron beams, ion beams, and X-rays[14a-c,e, 15-17].

At the present time, electron beam lithography is already widely used for the production of photomasks having very fine structures. A particular advantage of electron and ion beams is that they can be steered in a simple controlled manner. By this means using the beam it is possible to directly produce an image on a radiation-sensitive layer without a mask.

X-ray lithography has the advantage that it makes possible the irradiation of a large area in a simple manner, but is associated with the disadvantage of masks which are complicated to produce and radiation sources which today are still of low intensity. Which process will finally be used predominantly for the reproduction of small structures has not yet been decided.

The use of all these high energy radiation techniques requires resists that are sensitive and can be differentiated *i.e.* there must be sufficiently great differences in the properties of irradiated and non-irradiated areas, *e.g.* solubility. Of course, the chemistry of resists of this type differs completely from that of the conventional resists used for producing images with long wavelength UV light[4d,e, 8c, 13b].

Progressive miniaturization is accompanied by a demand for increasingly finer processing techniques: for example, the progressive replacement of wet etching processes, which give rise to pronounced under-etching because of their isotropic mode of action, by dry processes[14d, 18] (plasma and ion etching processes). These may be performed such that the etching is anisotropic, *i.e.* underetching of the resist layer is avoided.

Of course, resists may only be employed for dry etching processes of this type when removal of material from them is kept within reasonable limits of removal of material from the substrate.

A logical development of these considerations leads to the recently published photoresist techniques by means of which the development, the etching of the bared areas, and the removal of the resist mask are effected by a combination of thermal steps using plasma etching processes[19, 20].

The reduction in lateral size of the structures on a chip does not result in a proportionate decrease in the thicknesses of the structures. Thus, it is frequently necessary to differentiate resist layers whose height is substantially greater than the width of the structures to be resolved and which, moreover, are located on structured surfaces. Here, good results are obtained using so-called multilayer resist systems[14b, 20], which consist of at least two different resist layers but which can also be separated by an inert intermediate layer. A first non-radiation sensitive resist or a resist which in comparison to the second resist is sensitive to other radiation, serves as a leveling filling material for the vertical profile of the chip. The first resist layer is covered by an essentially planar second resist layer, which is very thin and thus permits high resolution; after structuring, this second layer represents an ideal mask in intimate contact with the layer below. The unprotected areas of this layer are solubilized by irradiation or are removed by an anisotropic plasma.

2.4. Production of Printed Circuit Boards

2.4.1. Subtractive and Additive Techniques

As already mentioned in the introduction, the printed circuit board has a double function: on the one hand it is the mounting base for all components and on the other it must carry the circuits between all components which are insulated from one another. A very large number of conductors have to be juxtaposed in close proximity to each other. In order to produce the conductor density required today in the more demanding printed circuit boards, it is

no longer possible to accommodate the circuitry on one level: Two or more levels are required, and these are insulated from one another and only have a conducting connection at certain points, *i.e.* "through-hole plating" is necessary (Fig. 10). Today multilayer boards contain up to about 30 circuit levels.

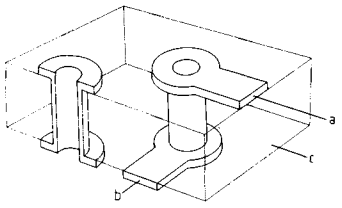


Fig. 10. Schematic view of "through-hole plating": A metal sleeve connects the circuit level (a) above the insulating board (c) and the circuit level (b) below the insulating board.

The production of a printed circuit board commences with its design, which today involves CAD methods, both for complicated printed circuit boards and integrated circuits. Using an electronically controlled photoplotter, the design in its original size is transferred onto a silver film, which can then serve as the photomask for the photoprinting process[21].

A large number of techniques for the production of printed circuit boards are known[22,23]. Three important ones are the *subtractive technique*[23], the *semi-additive technique*[23,25], and the *fully additive technique*[23,24].

In all these techniques, the production of printed circuit boards starts from a base material, in most cases an insulating sheet clad in the subtractive technique, for example, with a 35 μm thick copper film; with additive techniques the sheet carries a 20–30 μm thick insulating, adhesion-promoting layer, the so-called adhesive.

In the *substractive technique*, in the simplest case, a conductor is produced by applying a resist mask corresponding to the circuit onto the copper-laminated base material, followed by a process which etches away the unprotected copper. In the *fully additive technique*, for example, the adhesive layer is provided with a resist mask having apertures only in those areas of the adhesive surface on which the metallic, in most cases, copper circuit is to be formed. The circuit is selectively built up to the desired thickness exclusively by means of chemical deposition from copper baths[23].

In the *semi-additive technique* base material coated with adhesive is first provided with a thin conductive copper layer over the total surface of the adhesive in an electroless copper bath, and this copper layer is frequently reinforced electrochemically to a few μm. As in the case of the fully additive technique, a resist mask is now applied through whose apertures the conductors are then built up—in this case—electrochemically to the desired thickness *e.g.* 30–40 μm. After removal of the resist mask by treatment with an etching agent, the thin conductive copper layer is etched away in the so-called differential etching process; however, the height and width of the conductors are both reduced to roughly the same extent by the isotropically-acting etching medium. Typically, a complete series of process combinations and mixed processes characterize the steps in the various groups of procedures.

In many processes, non-conducting surfaces, *e.g.* adhesive layers and walls of drilled holes must also be coated with copper. This is achieved by roughening and subsequent activation processes using Pd or Cu catalysts for the electroless deposition of copper. The catalyst can also be incorporated into the adhesive and the insulating material of the base (core-catalyzed base material).

Table 1. Production of a through-hole plated printed circuit board having two circuit levels.

	Subtractive technique	Semi-additive technique	Fully additive technique
Base material	Insulating board laminated on both sides with copper (copper base)	Insulating board coated on both sides with adhesive	Insulating board core-catalyzed coated on both sides with adhesive containing catalyst
Drilling holes where through-hole plating is intended	+	+	+
Application of catalyst to the walls of the holes and, if appropriate, to the adhesive surface for electroless deposition of metal	+	+	–
Electroless deposition of copper (thin conductive copper layer), if appropriate, electrochemical reinforcement to a few μm of copper	+	+	–
Masking with a resist (photoprinting, screen printing, magnetography)	+	+	+
Activation of the catalyst in the adhesive and in the base material for electroless deposition of copper	–	–	+
Building-up the conductors by metal deposition			
electrochemical:			
copper	+	+	–
lead/tin	+	–	–
electroless:			
copper	–	–	+
Removal (stripping) of the resist mask	+	+	+
Copper etching	+	+	–
Solder reflow	+	–	–
Application of a solder mask	+	+	+
Hot air leveling	–	+	+

Table 1 gives a schematic comparison of the operations conventionally employed in the respective processes for the production of a through-hole plated printed circuit board having two circuit levels. For each process, one facet has been selected and described in a highly simplified manner. A large proportion of printed circuit boards are

produced today by resist techniques, predominantly by means of negative dry film resists. Printed circuit boards having circuit path diameters of between 250 and 150 μm and less and similar spacings—as predominantly used in the industrial electronics' sector (computers, telecommunications, *etc.*)—are almost without exception produced by this technique.

At first sight, comparison of the processes shown in Table 1 suggests that the fully additive technique is attractive, since copper is selectively deposited only where it is required. However, it has not yet been widely adopted in practice, because particular stages of the process are somewhat complex. To a lesser extent, the same also applies to the semi-additive technique. Today more than 90% of printed circuit boards are produced by subtractive techniques. Because of its great importance, a subtractive process is illustrated schematically once again for the very widely used metal resist technique (Fig. 11).

A special feature of this process is that the conductor regions, after the copper base has been masked with a resist, are built up electrochemically, firstly with copper and, on top of this, with a lead-tin layer that is stable to ammoniacal copper etching agents. After the resist mask has been stripped, the copper base is etched away and the lead-tin covering thus serves as an etch resist.

It is now customary, and, in the case of printed circuit boards having a high conductor density, also necessary to provide the printed circuit board with a solder mask which only leaves bare the lands at which the contacts of the components, *e.g.* integrated circuits, are soldered. The solder mask must therefore withstand a temperature of 260 °C for a few seconds. It remains a part of the printed circuit board. Solder masks, also, are now produced to an increasing extent by photoprinting process, *i.e.* a light-sensitive solder resist, *e.g.* a dry film resist, is applied to the whole surface, exposed imagewise, developed, and post-cured[26].

The subtractive process described in Figure 11 illustrates the advantages associated with the use of a rather thick dry film resist: on the one hand the drilled holes are covered over during lamination, and the resist does not penetrate these holes, from which it could only be removed with difficulty, and on the other, the regions in which the conductors are electrochemically built up are comparable to steep-walled ravines. As long as the electrochemical metal deposition takes place within the trough, spreading, and hence the danger of short-circuiting between conductors lying close together, is precluded.

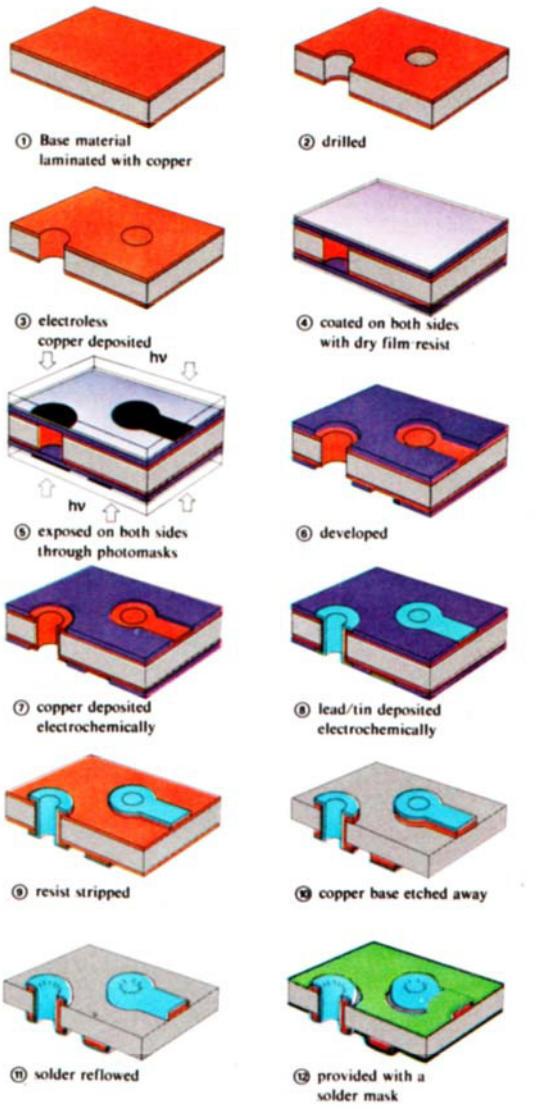


Fig. 11. Production of a through-hole plated printed circuit board by the metal resist technique, using a negative dry film resist. Through-hole plating is effected by drilling ②, at the desired points, through base material covered on both sides with 35 μm thick copper ①. The walls of the drilled holes are activated for electroless metal deposition, and a thin conductive copper layer ③ deposited using a chemical copper bath; this copper layer is frequently reinforced electrochemically by a few μm. After the component has been coated on both sides with a negative dry film resist ④, both sides are exposed through the appropriate photomasks, which are impermeable to light in the areas corresponding to the conductors and holes ⑤. After the support film has been peeled off and the photoresist developed ⑥ (dissolving away unexposed resist, the conductors in the planes and in the holes between the upper and lower sides are formed by electrochemical metal deposition: For example, with 30 μm copper ⑦ and on top of this *ca.* 10 μm lead-tin alloy ⑧. After removing (stripping) the resist mask ⑨, which is now no longer required, the bared copper base is first removed by means of an ammoniacal copper etching agent ⑩, and the solder on the conductive elements finally reflowed ⑪, *i.e.* after application of a so-called flux, the printed circuit board is heated to above the melting point of the lead-tin alloy, which then encases the conductors. In order to save solder and to prevent short circuiting between conductors in close proximity to each other, the printed circuit board is also provided with a solder mask ⑫, which covers the printed circuit board, apart from the lands.

2.4.2. Future Developments

The miniaturization trend in microelectronics has also extended to printed circuit boards. Thus, an ever-increasing number of contacts and conductors have to be accommodated on the same area. For the simple through-hole plated printed circuit board, this implies a transition from fine-circuit to ultrafine-circuit technique; conductor widths and spacings of 150 μm have already been produced, work on widths and intervals of 100 μm is in progress, and even smaller dimensions of down to 50 μm are under discussion.

This requires improved base materials and manufacturing techniques, and implies a still greater contribution from photoprinting in the future, together with increased use of the solder mask and possibly—owing to their better resolution—increased use of liquid resist techniques in the printed circuit board sector, which is presently dominated by negative to dry film resist methods.

Positive photoresists may also become important in future, since these not only have a particularly good resolution capacity but, in addition, produce resist coatings in the first photoprinting step which are still photosensitive and thus permit, in further photoprinting steps, other areas of the surface to be opened step by step for processing.

Increased use of additive techniques in the production of printed circuit boards may also be predicted, since the circuit path width and intervals decrease in size. Advantages in this respect are already provided by the semi-additive technique, because of the particularly low degree of lateral under-etching of the conductors when the conductive copper layer, which is only a few μm thick, is etched away. The fully additive technique is even more advantageous, since it involves no removal of material by etching steps, and thus no under-etching.

Currently, a number of processes are already being developed, which may one day substantially replace the classical printed circuit board. For example, one possible method uses a combination of photoprinting processes with electroless and electrochemical metal deposition to build up, step by step, three-dimensional circuit systems in which the originally photosensitive material remains a part of the finished element.

Similar to the procedure used in microlithography, in which the stored circuit design can be directly "inscribed" in a photoresist layer on the waver, it has also become possible in printed circuit board technology to directly transfer stored designs of circuit path levels from an electronic memory into a photoresist using a laser beam, *i.e.* without the intermediate stage of a film original[27]. Analogous techniques for the production of printing forms without the use of films have recently been reported[28].

3. Function and Chemistry of Photoresists

3.1. Introduction

In the majority of cases, photoresists are specifically designed multi-component systems which attain the required properties only when the individual components function cooperatively. Table 2 gives an idea of the variety of different requirements made of a photoresist.

Table 2. Important properties of industrial photoresists.

Solubility in suitable solvents
Long shelf-life in the absence of light
Good processing properties
Good adhesion to substrate
High sensitivity to differentiating radiation
Rapid development by non-toxic solutions
Exact transfer of the original, and reproducible, well-defined flanks upon development
Resist mask which is stable to etching, plating, and heat
Resist mask readily removable when no longer required

It is striking that no *single* resist or masking process is able to fulfill simultaneously all these requirements, which have to be further extended for special techniques; a large number of resists are required, each of which may be employed optimally in its own field. In this article it is only possible to select a number of systems in actual use, and describe their chemistry and mode of action. This review is supplemented by a few interesting novel chemical systems or application processes, whose practical relevance cannot yet be fully appreciated.

According to their change in solubility the systems are classified as "positive- or negative-working resists". This division into positive and negative systems is also limited to the photochemical systems which use light in the wavelength range from 300 to about 500 nm, and is, in addition, arbitrary in some cases, since systems are known which, depending on the procedure, can undergo "umpolung".

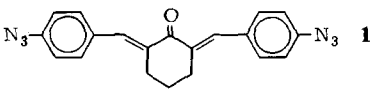
Resists that are sensitive to short wavelength UV light, electron beams, ion beams, and X-rays are summarized in Section 3.4, without regard to positive or negative function.

3.2. Negative-Working Photoresist Systems

The majority of photoresists used today are negative photoresists, *i.e.* systems whose solubility is reduced upon irradiation. A long road leads from the beginnings (*Niepce:* Syrian asphalt, 1826; *Talbot:* bichromate gelatins, 1852) to the photoresists which are now employed for the most demanding work. Only a few of the large number of systems which are theoretically suitable, and which have previously been reviewed many times[29], have proved useful industrially.

3.2.1. Photo-Crosslinking Systems

Diazide-Polydiene Systems: Today, negative photoresists for the production of integrated circuits use, almost without exception, partially cyclized polyisoprene as the crosslinkable component and a diazido compound as the photosensitive bifunctional crosslinking agent. A diazide of structure **1** is very commonly used: sulfazides are also used as crosslinking agents.



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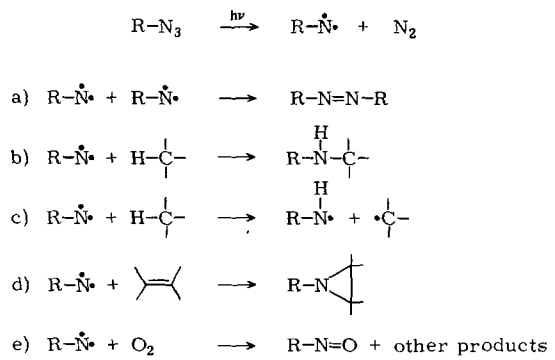
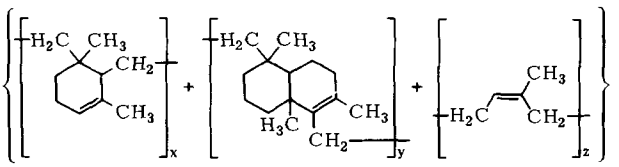
Upon irradiation, nitrogen cleaves off and the azide groups form very reactive nitrenes (R—Ṅ·) in both singlet and triplet states. The course of reaction given in Scheme 1 has been discussed[29i].



Scheme 1.

Singlet *and* triplet nitrenes undergo reactions a) and d); insertion reaction b) is a typical singlet reaction and reaction c) a typical triplet reaction.

The partially cyclized polyisoprene **2** is an ideal reactant for reactions b), c), and d) and is, in addition, a resist constituent which has a pronounced influence on the adhesion to substrates, and the mechanical and chemical properties, *i.e.* essential characteristics of the quality of the photoresist. Recently, photoresists based on partially cyclized polybutadiene and diazides have also become commercially available[30].



2

In reaction e), the ever-present atmospheric oxygen competes with the crosslinking reactions[31]. Photoresists of this type are therefore frequently irradiated under nitrogen.

Photodimerization Systems: Today a large number of photoresists use photodimerization for the crosslinking reaction. These include the now classical cinnamic acid derivatives and the structurally related chalcones. The particularly extensively investigated crosslinking reaction of cinnamic acid derivatives proceeds essentially as a photoinduced [2+2]-cycloaddition, and leads to formation of cyclobutanes[29c,32].

The systems are of industrial interest as photoresists when a polymer chain carries a large number of photodimerizable groups. For polyvinyl cinnamate, which is used industrially, these groups are produced by esterification of polyvinyl alcohol with cinnamoyl chloride. The direct free-radical polymerization of vinyl cinnamate is unsuccessful, owing to the tendency of this compound to undergo cyclopolymerization. Cationic polymerization of vinyloxyethyl cinnamate is possible[33]. Free-radical polymerization is also possible for compounds in which the cinnamoyl group and the reactive double bond cannot be directly linked[34]. Of particular industrial significance is the possibility of sensitizing cinnamic acid derivatives to relatively long wavelength light (up to *ca.* 500 nm) by triplet energy transfer[29c].

Recently, a type of photodimerizable epoxide resin **3**, which has been known for a relatively long time, has also been used as a photoresist[35,36].

The resins not only carry groupings capable of photocycloaddition, for example chalcone structures, but also epoxy groups, which permit suitably catalyzed thermal crosslinking. Systems of this type thus permit a resist mask to be initially produced in a photoprinting step, and then to be further crosslinked by heating. A typical application is the production of solder masks.

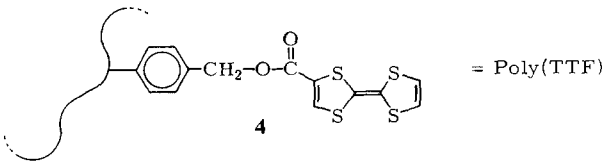
3.2.2. Systems Based on Photochemically Induced Polarity Changes

In the systems described in the previous section, preformed polymer chains crosslink to form a three-dimensional network upon irradiation.

Development is carried out using an organic solvent which not only dissolves the unexposed material but also swells the crosslinked areas to a greater or lesser extent.

The undesirable swelling can be substantially suppressed by converting the non-polar structural elements into, for example, ionic ones.

These systems are soluble in solvents of low polarity, such as ethers or ketones, before being irradiated but insoluble after irradiation[37]. An example is the combination of a polymer bearing tetrathiafulvalene groups **4** with tetrabromomethane **5**. The photochemical reaction is represented as a redox process leading to polar salt structures **6** in the polymers.



4

$$\mathbf{4} + CBr_4 \xrightarrow{h\nu} \text{Poly(TTF)}^+\ Br^- + \ldots$$

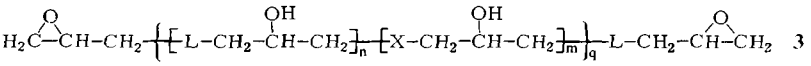
5 **6**

3.2.3. Photoinitiated Systems

The photoreactions mentioned in Sections 3.2.1 and 3.2.2 have quantum yields ≤ 1. To produce adequate crosslinking density, high intensity radiation and long irradiation times must be used. In order to use acceptable irradiation times, extremely thin resist layers (< 10 μm) are used in these systems.

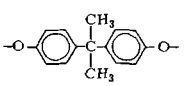
In photoinitiated processes a photoinitiator, which is present in low concentration, is electronically excited to form a reactive species, which initiates a chain reaction leading either to an increase in the size of the molecule or to crosslinking.

Photoinitiated Polymerization: Photoinitiated, polymerization processes, particularly those of the free radical type, which have been extensively investigated since the 1940's, are of industrial importance: The technical aspects and chemical principles of these processes have been treated in numerous reviews and monographs[29a,b,d-g,i,j,l,m].

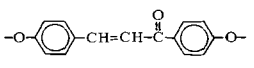


3

Scheme 2. X represents, *e.g.*



and L represents a photodimerizable moiety, *e.g.*



Systems of this type are used, in particular, as dry film resists[6,26]. Photopolymer materials used for this purpose contain a photoinitiator system, monomers, which are polymerizable by free radicals, and polymeric binders as the most important constituents. Furthermore, they may contain thermal polymerization inhibitors and modifying additives such as plasticizers, dyes, and adhesion promoters.

A very large number of photoinitiators or photoinitiator systems are known, which upon irradiation produce polymerization-initiating free radicals[38,39].

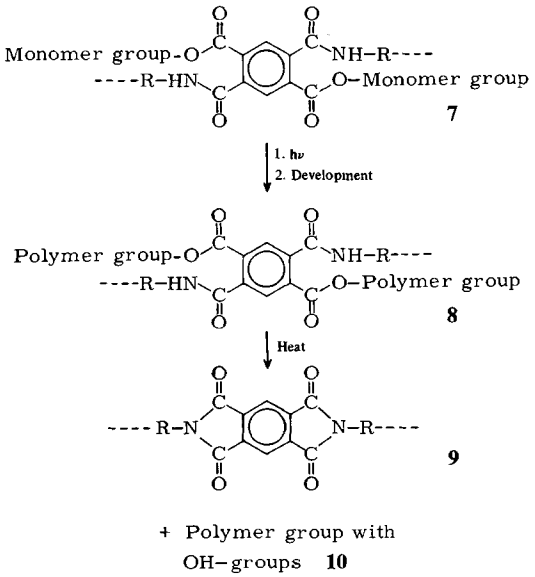
Radicals are formed by photofragmentation (benzoin ether), by transfer of electrons (benzophenone/aliphatic amine) or hydrogen atoms (anthraquinone/aliphatic ether). A few photoinitiator systems can be sensitized to light of relatively long wavelength[40,41].

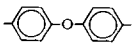
As monomers predominantly esters or amides of acrylic and methacrylic acids with polyhydric alcohols or amines, respectively, are used, *i.e.* compounds which are frequently liquids.

In addition to monomers, the solid layers must also contain compatible polymeric binders: these serve, however, not only as thickeners, but rather contribute some of the properties which the photo-hardened material should finally possess. The choice of binder also determines which type of developer (organic solvent or aqueous alkali) is to be used to develop the unexposed regions of the layers.

Since the photoinitiated free-radical polymerization is inhibited by oxygen, it is necessary to exclude oxygen as far as possible.

The systems based on photoinitiated polymerization also embrace the recently described principle for producing masks stable at high temperatures[42]. As shown in Scheme 3, the unexposed material contains soluble polyamide precursors **7** carrying polymerizable groups. During processing, the layers are first differentiated in a photo-

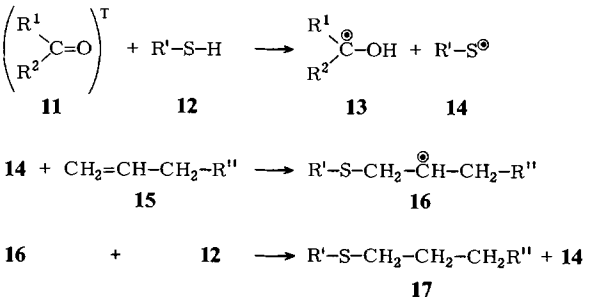


Scheme 3. R is, *e.g.* 

and the monomer group is, *e.g.* $-CH_2-CH_2-O-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{|}{C}}=CH_2$

printing step, *i.e.* non-crosslinked photoresist which has not been exposed to light is removed. Thereafter, the resist mask **8** is thermally converted into polyimide **9**; the polymerized groups **10** being split off. This type of photoresist is of particular interest for microelectronic applications.

Thiol-Ene Systems: In a photoinitiated free-radical chain reaction, thiols **12** form adducts with alkenes **15**, forming thioethers **17** (Scheme 4)[29i,43]. Examples of suitable photoinitiators are ketones.



Scheme 4. R^1, R^2 = aryl; R', R'': alkyl.

The radicals **13** can also initiate or interrupt chains, either by direct reaction or by abstracting hydrogen from the substrate.

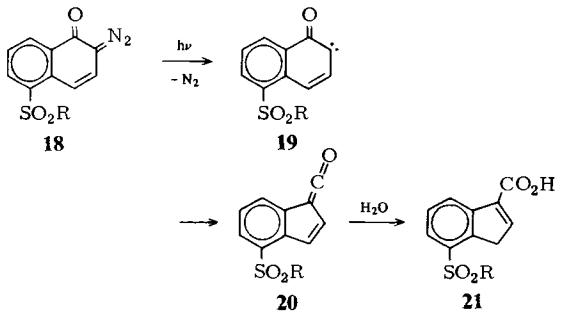
In order to obtain a high crosslinking density, thiols and alkenes containing numerous SH groups and CC double bonds, respectively, are used.

3.3. Positive-Working Photoresist Systems

In contrast to negative photoresist systems, the photochemical reaction does not change the original properties of the resist in positive resists; a change in solubility occurs only in the areas of the resist layer removed in the subsequent development step. The protective resist mask thus produced, if not deactivated thermally or by illumination, is still photochemically reactive and can, after undergoing a process step, be re-exposed and converted into a differently structured mask for a subsequent process. For this purpose, however, the resist must, at the outset, also possess all those properties required for the protective function, *e.g.* adhesion and "resistance", in addition to good, defect-free film formation and adequate photosensitivity. These requirements are obviously not easy to fulfill, since of the large number of systems proposed only a few appear to have prospects of industrial use: up to the present time, only one system is in use, of course in a variety of modifications.

3.3.1. Diazonaphthalenone Systems

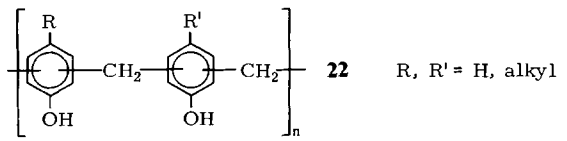
All positive photoresists used industrially on a relatively large scale are liquid systems which exploit the photoinduced Wolff rearrangement[44] of diazonaphthalenone derivatives (2-diazo-1-naphthalenones) **18**. According to more recent investigations the end product of the Süs reaction[45] is not 1-indenecarboxylic acid but 3-indenecarboxylic acid **21**[46]; ketenes, such as **20** have been confirmed as educts of the hydration, but it has not been possible to date[47] to detect carbenes **19**.



Scheme 5.

In addition to compounds of type **18**, only derivatives of diazooxonaphthalene-4-sulphonic acids are used in photoresists[5e] (R predominantly represents aryloxy groups, and occasionally substituted amino groups).

Scheme 5 illustrates a differentiation principle based on the conversion of the oleophilic compound **18**, which is insoluble in aqueous systems, into the alkali-soluble **21**; however, the situation becomes complicated in industrial resist formulations containing a binder of the novolac type (non self-hardening phenolic resin) **22**, in addition to the photosensitive component **18**.



22 R, R' = H, alkyl

In Figure 12 the situation is considered with respect to the solubility properties of this resin, which, owing to its phenolic hydroxyl groups, is partly soluble in dilute aqueous alkali solutions; its solubility is changed in a characteristic manner by certain additives.

The possibility of aqueous-alkaline development of photoresists of this type is one of the essential reasons for using this system to produce very fine structures on semiconductor surfaces and mask substrates: the hydrophobic nature of the unexposed resist elements prevents them from swelling during development. Troughs, whose widths are equal to the thickness of the resist layer, can still be produced.

For negative photoresists, a minimum value of the ratio of trough-width to layer-thickness of 3 : 1[4e] currently applies; for a given resist-layer thickness, the resolution obtainable with positive systems is therefore higher. A further advantage is that the photochemically unchanged resist mask can be more easily removed when it has fulfilled its function.

3.3.2. Photocatalytic Systems

Although positive photoresists based on diazonaphthalenone derivatives proved suitable for industrial use some time ago and are increasingly gaining ground over negative photoresists for the production of integrated circuits, they suffer from the same principal disadvantage as the systems mentioned in Sections 3.2.1 and 3.2.2: Since they are based on photochemical one-quantum

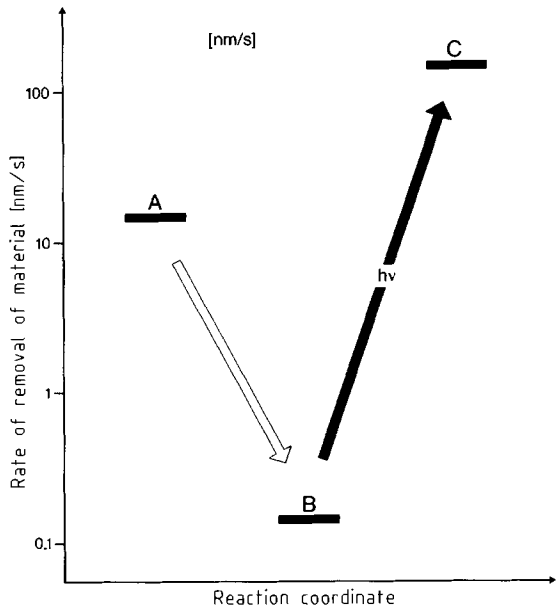
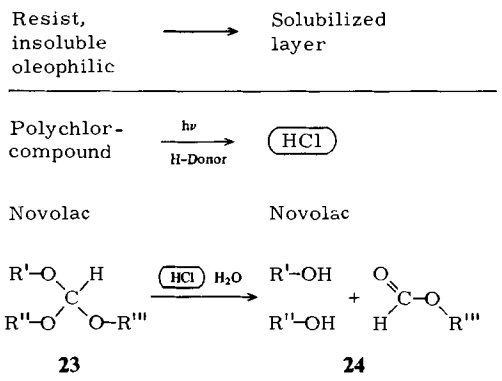


Fig. 12. Solubility changes of phenolic resins caused by additives. A layer of the phenolic resin **22** is removed at a rate A by an aqueous-alkaline developer of particular concentration. The incorporation of a diazonaphthalenone derivative into the resin layer reduces the rate of removal considerably (B), presumably *via* an association in which the phenolic hydroxyl groups of the resin participate. Photolysis cancels out this association; acid **21** formed in the ubiquitous water is neutralized by the developer, and increases the solubility drastically (C). The numerical values [48] of the ordinate are very dependent on the experimental conditions [49] and are intended only to represent the order of magnitude of the solubility changes.

processes, their photosensitivity can be manipulated only within relatively narrow limits. This problem is particularly evident with relatively thick layers, since the photochemical reaction must also involve the lower regions of the layer close to the substrate to ensure that the resist becomes soluble throughout. In addition to the amount of light required, the absorption properties of the layer constituents must, therefore, also be taken into account. These restrictions may be removed by using systems which, like photoinitiated processes in negative systems, produce a catalyst upon irradiation of a photoreactive, absorbing compound present only in low concentration; this catalyst in turn initiates the modification of a second, photochemically inert compound which does not absorb in the actinic region. Thus, the important functions in diazonaphthalenone derivatives, namely photoreactivity and inhibition of solubility, are separated. Suitable catalysts are hydrohalic acids which may be readily generated photochemically from photosensitive polyhalogen compounds; suitable modifiable solubility inhibitors are *e.g.* acetals of aromatic hydroxy compounds or *O,N*-acetals of *N*-alkylarylsulfonamides[50a], aliphatic polyacetals[50c], orthoester—and amide acetals[50b], polymeric orthoesters[50f], enol ethers[50d], and acyliminocarbonates[50e] all of which readily undergo acid-catalyzed hydrolysis[51].

While in some of these compound classes hydrolysis products of relatively high acidity—phenols and *N*-alkylarylsulfonamides are formed, which themselves are soluble in alkali—the aliphatic polyacetals and orthoesters are hydrolyzed to neutral alcohols. However, the photosolubilizing process described in Section 3.3.1 may, in principle, be extrapolated without restriction if the decrease in the rate

of removal of material (B) in Figure 12 is caused by a hydrophobic inhibitor instead by a diazonaphthalenone derivative, and the increase (C) is caused by a hydrophilic hydrolysis product instead by an indenecarboxylic acid derivative (Scheme 6). The inhibition of the solubility by the educts may be explained by assuming that the phenolic hydroxyl groups of novolak are blocked by hydrogen bonds to the ether oxygen atoms of the inhibitors. In contrast, the hydrophilic low-molecular weight hydrolysis product **24** acts as a cosolvent for the aqueous alkaline developer. Scheme 6 clarifies the relationships.



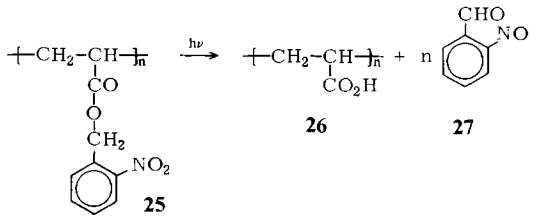
Scheme 6.

Particularly suitable polyhalo compounds are 2-styryl-[52a] and 2-aryl-4,6-bis(trichloromethyl)-*s*-triazines[52b], whose UV absorption maxima span the wide range from <300 nm to >440 nm, depending on the substituents on the aryl moiety. Of the large number of substances from which acids can be produced photolytically, this class of compounds fulfils the requirement of high effectiveness particularly well, *i.e.* of high resist "photosensitivity", together with thermal and solvolytic stability; this is necessary to prevent premature solvolysis of the inhibitor. The substituents R of the orthoester **23** shown in Scheme 6 can be parts of polymer chains, so that the hydrolysis has the effect of reducing the molecular weight at the same time.

Using the principles described, positive-working dry resists may be produced which, even for layer thicknesses of >50 μm, can still be solubilized with industrially acceptable amounts of light. Thick layers of this type, containing diazonaphthalenone derivatives are less photosensitive by at least one order of magnitude.

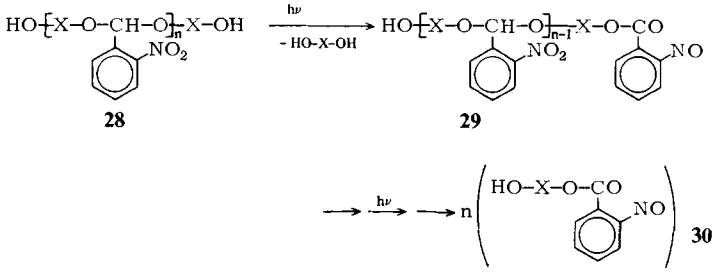
3.3.3. *o*-Nitrobenzyl and -Benzal Systems

How advantageously even classical photochemical reactions[53] can be used in modern photoresists may be illustrated by the following three systems, all of which utilize the migration of an oxygen atom from an electronically excited nitroarene to the α-C atom of a side chain in the *ortho*-position. The compounds most likely to be used industrially, particularly for dry film resists, appear to be polymers **25** containing *o*-nitrobenzyl acrylate moieties, which can be split photochemically[54] into acrylic acid units **26** and *o*-nitrosobenzaldehyde **27** (Scheme 7). Because the free carboxyl groups produced, those parts of the layer exposed to light may be removed by alkaline solvents.



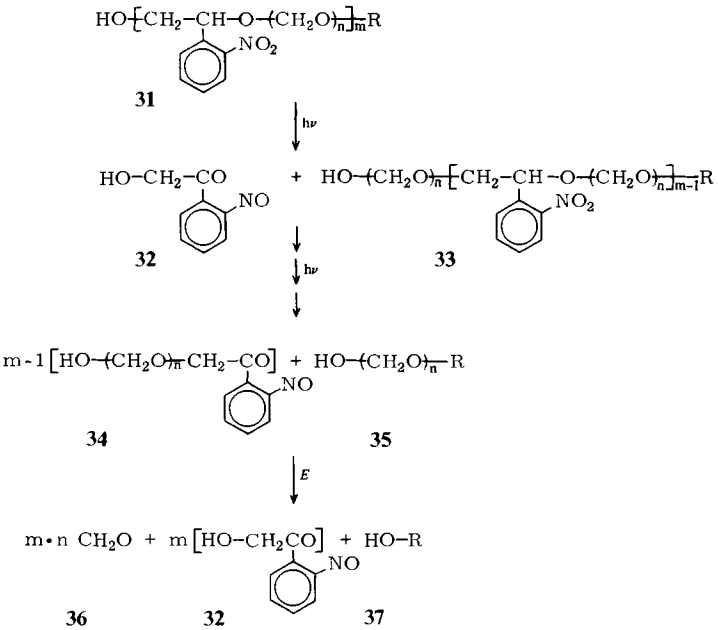
Scheme 7.

Another system[55] (Scheme 8) uses polyacetals **28** obtained from aliphatic diols and *o*-nitrobenzaldehyde. Since in this case no acid groups are formed photolytically, development must be carried out using organic solvents *e.g.* 2-ethoxyethanol. The differentiation is based on solubility differences between the unexposed layer areas containing intact polymer units and the more readily soluble fragments **30** at the exposed points.



Scheme 8.

In Scheme 8, X represents the alkylene group of a diol, *e.g.* 1,4-cyclohexanedimethanol. In principle, the third system[56] (Scheme 9) even offers the possibility of "dry", solvent-free development. The exposed areas can be developed by treatment with organic or inorganic bases, or simply by heating; this leads in **34** and **35** to depolymerization of the polyoxymethylene partial chain which is no



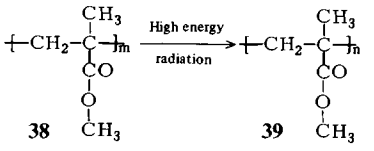
Scheme 9. *E:* Development by action of heat or basic solvents.

longer end-capped after photofragmentation. 1,2-Glycol or 1,3-propanediol moieties, which carry an *o*-nitrophenyl group on at least one of the terminal C atoms, are inserted into the polyoxymethylene chains. In polymer **31**, R represents a unit which blocks the polyoxymethylene chain, *e.g.* an acyl group or even an *o*-nitrophenyl(hydroxyethyl) unit.

3.4. Resists Sensitive to Short Wavelength UV Irradiation, Electron Beams, X-Rays, and Ion Beams

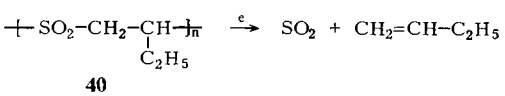
The photochemistry of photoresists sensitive to electromagnetic radiation of wavelengths $\lambda > 300$ nm is, in general, well understood. Selective reactions cause clearly predictable solubility changes in the resist material. However, relatively high-energy radiation excites isolated double bonds, nonbonding electron pairs and σ bonds, in addition to conjugated π bond systems. Ionizing radiation, *i.e.* electron beams, X-rays, and ion beams, produces reactive intermediates, whose secondary reactions are not very selective and which are more similar to thermal than photochemical processes. Structural differences in the irradiated compounds, which at first sight appear small, steer the reaction in the direction of fragmentation or depolymerization (positive procedure), or towards graft polymerization and crosslinking processes (negative procedure). Frequently both processes occur side by side, and can be influenced by the radiation dose.

High-molecular weight polymethyl methacrylate **38** is a resist which can be differentiated by all four types of radiation mentioned. Short wavelength UV radiation, in the range 230 nm to 280 nm, which today is largely accessible industrially, induces, *via* $n \rightarrow \pi^*$ excitation of the carbonyl group, fragmentation to lower-molecular weight fragments **39** that are more readily soluble than the starting polymers. The same result may be obtained using ionizing radiation and X-rays, whose action is based on the photoelectrons emitted after absorption of the primary radiation.



38 high molecular, sparingly soluble — **39** low molecular, readily soluble

Owing to its high-resolution potential and its good processing properties, the readily obtainable polymethyl methacrylate is used industrially as a positive electron beam resist, although its sensitivity to radiation leaves something to be desired[57]. Another more sensitive positive electron beam resist is polyethylethylene sulfone ("polybutene sulfone, PBS") **40**.



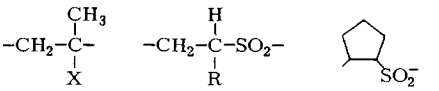
40

Irradiation of **40** with electrons causes at least partial depolymerization into the volatile comonomers SO_2 and 1-butene. It is therefore possible in certain applications to produce the resist relief directly, *i.e.* "dry" and without a special developing step[58]. Positive electron-beam resists also include diazonaphthalenone-based resists, which are, however, of low sensitivity[4e,59].

The copolymer of glycidyl methacrylate and ethyl acrylate is an example of a negative-working electron beam resist.

The structural characteristics that control the positive and negative behavior in a polymeric electron-beam resist are shown in Scheme 10.

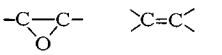
Positive electron-beam resists



X = CO_2R, COR, CN, phenyl etc.

R = alkyl

Negative electron-beam resists



alkyl-, haloalkyl- and aryl-group

Scheme 10.

Similar structural units, which in most cases also contain elements of higher atomic number, *e.g.* halogen atoms to increase the absorption coefficient, are also found in X-ray resists[4e,60,61].

To date, the field of ion beam resists[15e] has been investigated only to a small extent, but as already mentioned the pertinent chemical principles should be similar to those for resists that are sensitive to X-rays and electron beams. However, ion beams also make it possible to produce inorganic-organic or pure inorganic resist-masks by selectively implanting ions in certain regions of an organic polymer layer or of a silicon dioxide layer. The less resistant, untreated zones are etched away in a subsequent plasma process.

It is not yet possible to foresee what resists will finally be used in the new, fascinating processes and to what extent these processes themselves will be employed in the production of electronic components. It is possible that the use of short wavelength UV radiation, as a "photooptical" process closely related to known technologies, will dominate in the medium term. However, in spite of a large number of systems which are in principle suitable, there is a lack of resists which fulfill all the requirements[13b,62]. The concept of combining the binder and the photoreactive component, which is successful in the long wavelength region, is greatly limited by self-absorption (below $\lambda = 300$ nm) of the binders suitable for classical photoresists and which have proved useful in the manufacturing processes.

4. Prospects

The very rapid advance of microelectronics in the industrial, public, and private sectors is illustrated by the data in Table 3[63], which applies exclusively to the market in "integrated circuits" (in millions of dollars).

Table 3. Size of the integrated circuit market (in million dollars).

	1981	1982 (estimate)	Increase [%]
USA	5351	6558	22.6
Japan	3797	4603	21.2
Europe	1498	1690	12.8

Although predictions[64] should be treated with reservation, even conservative estimates up to 1991 assume an inflation-corrected average growth of 8–9% per year.

Miniaturization of circuits has not yet reached insurmountable physical barriers; however, to utilize the remaining margin, new materials and processing methods must be developed. The service function of photolithography—the term includes the use of generally radiation-sensitive resists—will continue to have an important position for a long time. It will also certainly not be possible to dispense with the conventional semiconductor materials in the immediate future. In spite of all efforts, "molecular circuits"[65] based on proteins or non-biological polymers, such as polyacetylene, are still things of the future. The dimensions of circuit elements of this type could shrink to that of the molecular scale (*ca.* 100 nm).

It is uncertain as to whether attempts of this type will finally mature into a practicable technique. In a technique of this type, classical photolithography, if at all, would play only a peripheral role, but chemistry would continue to play a key role, even if in a different way.

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The Chemical Behavior of Multibridged [2$_n$]Cyclophanes**

By Jürgen Kleinschroth and Henning Hopf*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

Multibridged [2$_n$]cyclophanes comprise a novel class of aromatic compounds, in which two benzene rings are connected by three up to a maximum of six ethano bridges. Compared to classical nonannelated arenes, their most distinct chemical property is the ease with which, particularly the higher-bridged homologs, take part in addition reactions (Diels-Alder additions, hydrogenations, and ionic additions). On the other hand, the typical regenerative behavior of aromatic molecules is not fully suppressed in the [2$_n$]cyclophanes as evidenced by such typical electrophilic aromatic substitution reactions as bromination, Friedel-Crafts acylation, and nitration. Besides these reactions in which the benzene rings are either destroyed or retained, reactions at and with the ethano bridges, *e.g.* their cleavage, isomerization, and functionalization can also occur.

1. Introduction

On extraction of polymeric compounds produced by high-temperature pyrolysis (900 °C) of *p*-xylene, *Brown* and *Farthing* in 1949 isolated minute amounts of a hydrocarbon to which they assigned the structure tricyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene (**1**, Scheme 1) from an X-ray structural analysis[1,2]. Since "conventional methods", not described in further detail, failed to reproduce this compound with the trivial name di-*p*-xylylene, the authors concluded that the ring-strain evidently present in the molecule could only be overcome by the extreme reaction conditions of the pyrolysis. That this is, in fact, not at all the case was shown, however, only two years later by *Cram* and *Steinberg*, who prepared **1** by Wurtz-coupling 1,2-bis-(4-bromomethylphenyl)ethane, although the total yield did not surpass 2.1%, even under high-dilution conditions[3]. After *Cram*, **1** and its homologs, which may be prepared by similar (and other conventional) methods, are termed [m.n]paracyclophanes with m and n symbolizing the number of CH_2 groups bridging the benzene rings, the prefix describing the anchoring points of the bridges, and the stem of the name resulting from a contraction of *cyclo*, *ph*enyl, and alk*ane*[4]; according to this nomenclature, hydrocarbon **1** is designated [2.2]paracyclophane[5].

In this first publication *Cram*[3] not only laid the basis for a new group of aromatic compounds but also mentioned most of the reasons that make cyclophanes even today, thirty years later, a much studied class of compounds: The transannular interactions between the benzene rings, which are particularly pronounced when the molecular bridges are short and when one arene-half carries electron donor, the other electron acceptor substituents[6]; the deformation of the benzene rings, which—depending on the type of phane molecule—may be either boat- or chair-like[7a,b]; bond lengths and angles deviating from the norm, and, finally, the many possibilities of generating molecular asymmetry using derivatives of **1**[8]. Phane molecules, in

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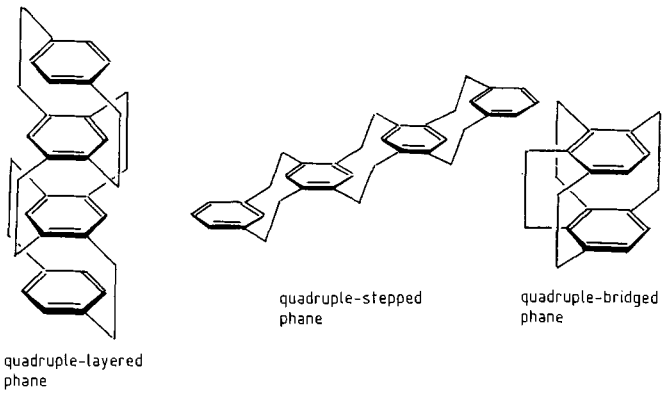
[**] Cyclophanes, Part 15.—Part 14: S. H. El-tamay, H. Hopf, *Tetrahedron Lett. 1980*, 4901.

which all types of aromatic subunits are bridged by polymethylene chains but also by functionalized bridging units are known today in large numbers[9].

As far as the parent systems, which only contain benzene rings and ethano and propano bridges, are concerned present research activities are focused on multilayered[5, 10], multistepped[9e, 11], and multibridged cyclophanes[9e, 12].



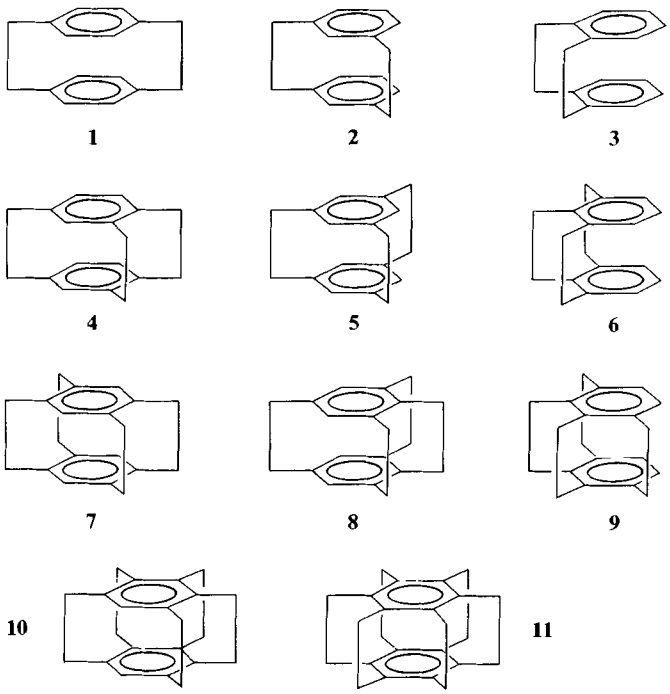
Whereas the first phane-type is of interest because its stacked or columnar structure allows electronic interactions over unusually large distances, and the relatively flexible multistepped phanes have been studied because of their dynamic properties, the multibridged phanes are structurally remarkable since they possess a "hollow" interior, into which in principle other chemical species, be they atoms or complete molecules, may be incorporated. Among the multibridged cyclophanes, the [2$_n$]cyclophanes "with parallel bridges" (see Section 2) represent the simplest type; for a comparative study of chemical reactivity it is important that during the last few years it has been possible to synthesize the complete series of all possible hydrocarbons of this type.

This review summarizes the chemical properties of these unusual arenes for the first time. The syntheses leading to these substances will, however, not be described again, since all the pertinent information may be found in a recent review article[12].

2. Multibridged Cyclophanes

2.1. Some Remarks on Nomenclature

All hydrocarbons composed of at least two aromatic systems held together by three or more ethano bridges will be called multibridged [2$_n$]cyclophanes. Evidently, the maximum number of the bridges depends on the size of the aromatic subunits. The bridges may either be in "parallel" or in "non-parallel" alignment. Whereas in the former case they are anchored to identical positions of the aromatic nuclei, in the latter they are not. The number of all possible cyclophanes with two benzene rings and parallel ethano bridges is easily determined: it corresponds to the number of the identically substituted benzene derivatives. Hence, there exist three [2$_2$]cyclophanes: [2.2]para- **1**, [2.2]meta- **2**, and [2.2]orthocyclophane **3** (dibenzocyclooctadiene); three [2$_3$]cyclophanes: [2.2.2](1,2,4)- **4**, [2.2.2](1,3,5)- **5**, and [2.2.2](1,2,3)cyclophane **6**; three [2$_4$]phanes: [2.2.2.2](1,2,4,5)- **7**, [2.2.2.2](1,2,3,5)- **8**, and [2.2.2.2](1,2,3,4)cyclophane- **9**, and, of course, one five- and one sixfold bridged molecule: [2.2.2.2.2](1,2,3,4,5)- **10**, and [2.2.2.2.2.2](1,2,3,4,5,6)cyclophane **11** ("superphane").



Scheme 1. [2$_n$]Cyclophanes with parallel ethano bridges.

2.2. Possible Reactions

The whole series of hydrocarbons **4**—**11** is in the meantime known[12]. The maximum number of systems with non-parallel bridges[13] may also be readily derived. However, it is more difficult to predict which of these molecules is stable under normal laboratory conditions; according to molecular models some of the "skew" phanes are very strained; they should therefore be much more reactive than the occasionally sluggish cyclophanes **4**—**11**.

Formally the [2$_n$]cyclophanes consist of the building blocks methylene bridge and benzene ring, and in principle two types of reactions could be discussed: those that take place at and with the ethano bridges, and those occuring at the benzene rings. The clear separation of these centers of reactivity is convenient to organize the experimental results; however, some reactions like the Lewis-acid catalyzed isomerizations (see Section 3.2) involve both parts of the molecule. The chemical behavior of the parent molecule **1** is discussed only in a cursory fashion on the following pages, since the whole spectrum of reactions of this hydrocarbon and its simple derivatives has been the subject of several review articles[9].

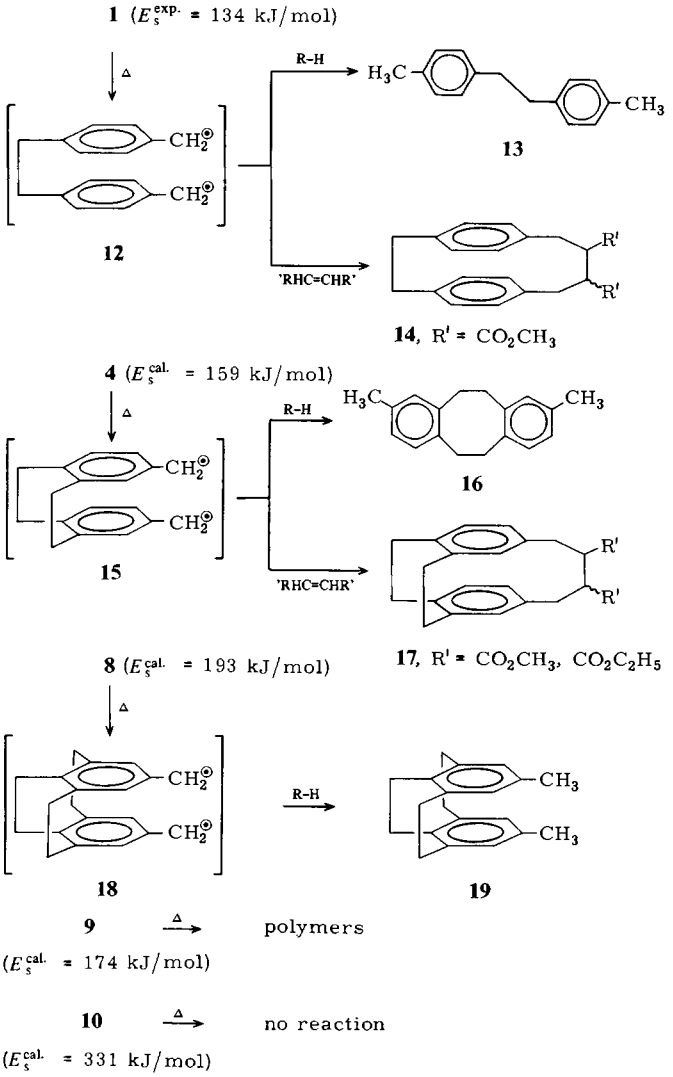
3. Reactions at the Ethano Bridges of [2$_n$]Cyclophanes

So far three types of reactions involving the ethano bridges have been observed: cleavage, shift, and functionalization. The cleavage reaction principally takes place between the benzene ring and the ethano bridge or between the methylene groups.

3.1. Radical Cleavage

Homolysis of the C_2-bridges may be initiated thermally or photochemically. In the simplest case of [2.2]paracyclophane **1**, pyrolysis at temperatures above 200 °C in the presence of hydrogen donors like *p*-diisopropylbenzene or thiophenol leads to 4,4′-dimethylbibenzyl **13** (21 and 74% yields, respectively). Evidently the diradical **12**, which may also be trapped by dimethyl maleate or dimethyl fumarate yielding the ring-expanded cyclophane **14** (200 °C, 40 h, 60%) serves as a precursor[8,14]. Interestingly—and supporting the diradical nature of the intermediate—both the yield of **14** and its isomeric composition are practically independent of the configuration of the trapping reagent.

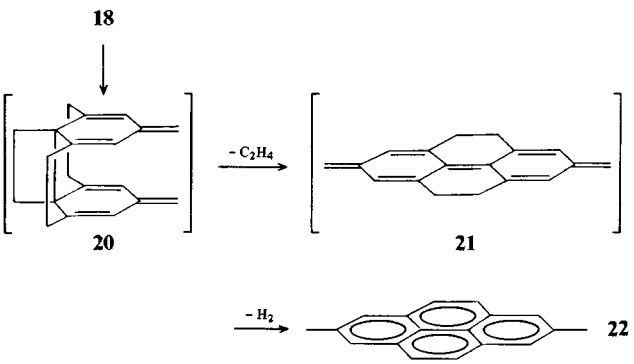
The next higher homologs **4** shows a similar behavior:



Scheme 2. Pyrolysis reactions of [2$_n$]cyclophanes.

The pyrolysis in thiophenol (22 °C, 73 h) or *p*-diisopropylbenzene (270 °C, 40 h) affords only 2,9-dimethyldibenzo[*a*,*e*]cyclooctadiene **16** (88 and 63%, respectively), and trapping experiments with diethyl maleate (220 °C, 43 h, 42%) and diethyl fumarate (220 °C, 72 h, 51%), or dimethyl maleate (250 °C, 40 h, 74%) lead to mixtures of the isomeric [2.2.4]cyclophane diesters **17**, although the reaction conditions are slightly more vigorous than for the homolysis of **1**[15]. That of the three possible ethano bridges the one indicated in Scheme 2 breaks, has been attributed to the greater strain release in the formation of diradical **15** than for alternative pathways[15a].

At first glance the [2.2.2.2]cyclophane **8** does not show any novel behavior: heating for 65 hours at 290 °C in *p*-diisopropylbenzene cleaves it to give the [2.2.2](1,2,3)cyclophane **19** (31%), *i.e.* the isolated ethano bridge is again cleaved[16]. However, only a slight increase in temperature and reaction time (300 °C, 75 h) suffices to force the pyrolysis along a completely different pathway. Under these more extreme conditions **18** is transformed into 4,9-dimethylpyrene **22**, the only solid reaction product of the pyrolysis[17].



Recyclization of the diradical **18** could now lead to the polycycle **20** which, *via* successive loss of ethene (formation of **21**) and hydrogen to yield **22**, finds a new way of stabilizing itself. **9** is considerably more thermally stable than **8**: after 65 h at 290 °C, and even 12 h at 400 °C this hydrocarbon is recovered unchanged from the pyrolysis-trapping experiment. Only above 470 °C (12 h) does **9** begin to decompose to polymeric products, possibly *via p*- or *o*-quinodimethanoid intermediates[16]. The pinnacle of thermal resistance is finally reached with superphane **11**, which is neither reductively cleaved nor undergoes ring expansion with diethyl maleate after 24 hours at 350 °C[18].

Scheme 2 also lists the strain energies of the [2$_n$]cyclophanes[19] (calculated except for **1**). The data show that both thermal stability and strain energy increase with the number of ethano bridges, indicating that the steady increase in ground state energy on proceeding from **1** to **11** is outmatched by the increase in the energy of the transition states leading to the various diradicals. This seems reasonable, since the spatial separation of the diradical centers to a distance that allows a chemical reaction to take place, whether this is hydrogen abstraction or addition to a double bond, necessarily must become more difficult if the two molecular halves undergoing separation are held together by additional molecular clamps. In other words: in molecules of this type—and presumably in other

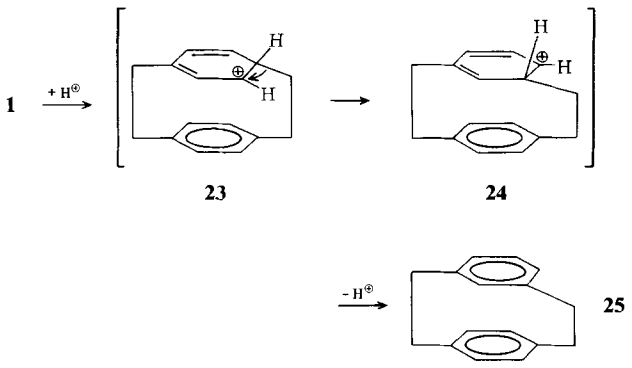
highly symmetrical hydrocarbons as well—several, and in the limiting case possibly all of the appropriate C—C bonds have to be stretched to the bond breaking distance to generate an interceptable intermediate. It may well be that the ring expansions mentioned are also of preparative value in other areas of hydrocarbon chemistry; *e.g.* pyrolysis of cubane in an unsaturated ester might well afford derivatives of basketane.

Both **12** and **18** have been generated and observed directly by irradiation of **1** and **8**, respectively, in a glassy matrix of 2-methyltetrahydrofuran at 77 K; the UV/VIS and fluorescence spectra of both species measured under these conditions constitute the first spectroscopic evidence for the formation of diradicals in photocycloreversions[20].

Irradiation of **1** in acetone, which serves both as solvent and sensitizer, at room temperature with a medium pressure mercury lamp leads to *p*-ethylbibenzyl exclusively, *i.e.* under these conditions scission between the benzene ring and the methylene group occurs[21].

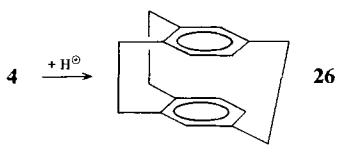
3.2. Ionic Cleavage

The experimental results on the ionic cleavage of the ethano bridges in [2_n]cyclophanes are presently rather heterogeneous, in particular hardly any comparative studies have been performed. The Lewis-acid catalyzed isomerizations belong to the better studied reactions. Treatment of

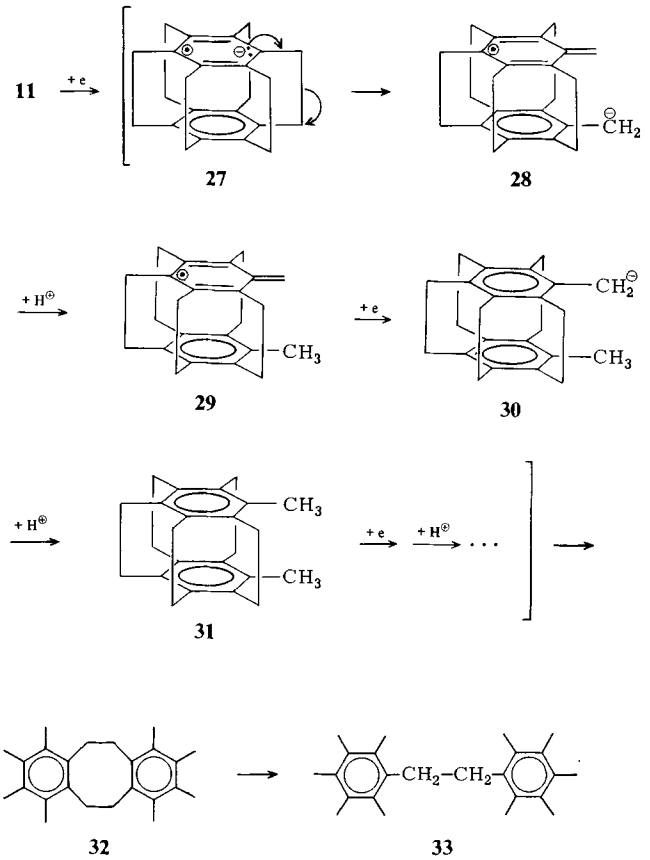


the parent compound **1** with $AlCl_3$/HCl in CH_2Cl_2 at 0 °C provides a mixture of hydrocarbons, from which *inter alia* [2.2]metaparacyclophane **25** may be separated in 44% yield[13].

The driving force for this reaction, which presumably takes place *via* the σ-complexes **23** and **24** is most likely provided by the reduction of the strain energy (E_s of **1**: 134 kJ/mol; E_s of **25**: 100 kJ/mol[19]). Among the higher bridged [2_n]cyclophanes only **4** has so far been induced to undergo a similar isomerization: after 30 min at −10 °C (CH_2Cl_2, $AlCl_3$/HCl) it affords the "skew" hydrocarbon [2.2.2](1,2,4)(1,2,5)cyclophane **26** (44%). Under the reaction conditions no further rearrangement takes place[16]. In



contrast, **8** and **9** do not even isomerize under more severe conditions (3 h, 25 °C). Although the intense red color that forms when HCl is added to the reaction mixture signalizes that a σ-complex is formed, a Wagner-Meerwein rearrangement evidently does not take place[22]. Molecular models indicate that in the triply-bridged cyclophane **4** the two benzene rings may be displaced towards each other during the migration of the ethano bridge, causing a reduction in molecular strain, whereas in the case of **8** and **9** such a displacement would cause a prohibitively large increase in strain. Related to these isomerizations is the first step of the *ipso*-substitution of **8** discussed in Section 4.

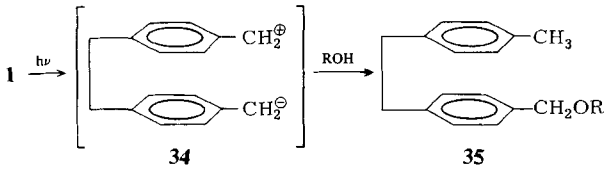


Scheme 3. Reductive cleavage of the ethano bridges of superphane **11**.

An anionic cleavage of the C_2-bridges takes place when superphane **11** is reduced with lithium/ethylamine in *n*-propylamine to form **32** (57%) and **33** (7%) (Scheme 3)[18a].

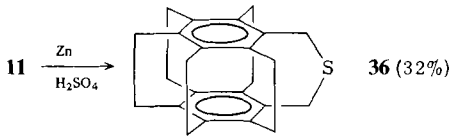
A plausible mechanism for this reaction is shown in Scheme 3. Radical anions like **27** correspond to the intermediates commonly discussed for the Birch reduction (see Section 4.2), and the cleavage of a bridging bond in [2.2]paracyclophane **1** by sodium/ammonia/ethanol to afford 4,4'-dimethylbibenzyl is well known[23]. The hexamethylbenzene dimer **33** is presumably formed by reduction of **32**.

The only report of a heterolytic destruction of a C_2-bridge in one of the molecules **1**—**11** concerns [2.2]paracyclophane itself, which on irradiation ($\lambda = 253.7$ nm) in alcohol is converted into the ether **35** *via* zwitterion **34**[21]:



34 35

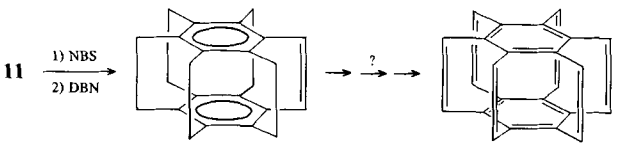
An unusual ring expansion is observed when **11** is treated with zinc in concentrated sulfuric acid (1 h). This reaction, of unknown mechanism, seems to be typical of superphane, since none of the other multibridged cyclophanes investigated so far yields products comparable to the thioether **36** if subjected to similar reaction conditions[18b].



36 (32%)

3.3. Functionalization

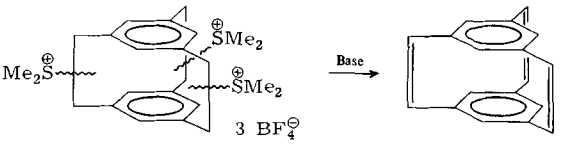
[2_n]Cyclophanes which are bridge-functionalized, *e.g.* with olefins, ketones, or epoxides, are of preparative, mechanistic, and spectroscopic interest; unfortunately, however, there exists a wide gap between attractive target molecules and their synthetic realization. For example, the monoolefin **37**, prepared from **11** by routine methods—bromination with *N*-bromosuccinimide (NBS) and subsequent elimination with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) might be regarded as the first step towards the hexaene **38**. But the low yield of only 20% is certainly not encouraging[18].



37 (20%) **38**

Hydrocarbon **38** is an electronically very unusual molecule since it is formally composed of a "core" containing 12 π-electrons (the two aromatic π-systems penetrate each other) and an orthogonal "sheath" possessing the same number of π-electrons. Overlap between the p-orbitals of the six olefinic double bonds could take place as in barrelene (bicyclo[2.2.2]octatriene).

The synthesis of the triene **40**, which corresponds to **5**, was accomplished by threefold Hofmann elimination of the trissulfonium salt **39** using *n*-butyllithium in tetrahydrofuran[24].



39 **40** (71%)

4. Reactions at the Benzene Rings

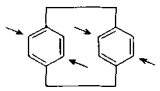
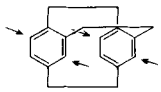
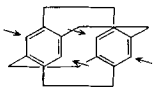
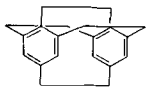
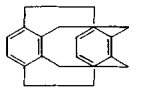
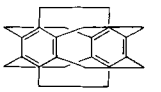
Even in their first publication *Brown* and *Farthing* discussed the non-planar geometry of the benzene rings in [2.2]paracyclophane **1**[2]. As shown by a later, more detailed X-ray structural analysis by *Lonsdale et al.*[25], at 291 K the bridgehead carbon atoms are displaced by 16.9 pm (14°) from the plane that passes through the remaining four aromatic carbon atoms. In other words, the benzene rings of **1** have a boat configuration. In the meantime, similar deformations have also been observed for **6**[26], **7**[27], **8**[28], **9**[29], and **10**[30]. Independent of the type and degree of the "deformation"[9b], the overlap of the six p-orbitals in a nonplanar benzene ring cannot be as effective as in benzene itself. In turn, a perturbation of the cyclic conjugation should affect the chemical and physical, and in particular the spectroscopic properties of these molecules[9]. It may, therefore, be asked whether the regenerative behavior so characteristic of the "classical" $(4n+2)\pi$-systems is displaced by an additive tendency in non-planar arene compounds, whether there is a competition between these two reaction modes, or whether the normally strongly disfavored addition is at least facilitated. Considering this background, which is also of theoretical interest[31], it is not surprising that most reactions performed with **4**—**11** have been addition reactions.

4.1. Diels-Alder Additions

In contrast to the readiness of conjugated di- and trienes to participate in [2+4]cycloadditions as diene components, simple aromatic 6π-electron systems are normally extremely sluggish in Diels-Alder additions—one reason for the use of benzene, toluene, the various xylenes, and halobenzenes as solvents in these reactions. Despite the low reactivity of *e.g.* benzene, 6π-arenes can react as dienes if the reaction is performed at high temperatures or in presence of Lewis acid catalysts; reactive dienophiles also add[32]. Nevertheless, the "superdienophile" 4-*N*-phenyl 1,2,4-triazoline-3,5-dione **41** does not add to benzene or any of the polymethylbenzenes at room temperature after several weeks[33]. If these molecules are incorporated into a [2_n]cyclophane system, however—*i.e.* [2.2]paracyclophane **1** as a formal dimer of *p*-xylene, superphane **11** as a dimer of hexamethylbenzene—then, in certain cases a drastic increase in the rate of addition is observed. As the data in Table 1 show[33], **1** and **41**, for example, react to afford the 1:2-cycloadduct after *ca.* six days at room temperature (the positions of the new bonds are marked with arrows).

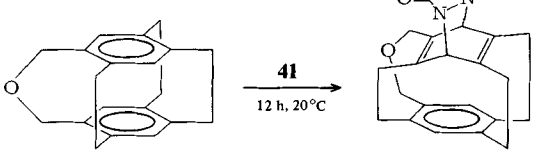
The incorporation of further bridges—cf. **4** and especially **7**—then causes an extreme increase in reaction rate: in the presence of [2_4](1,2,4,5)cyclophane **7** the intense red color of **41** vanishes within a few seconds—in other words, in its ability to add this double 6π-system it can compete with acyclic polyolefins! Comparable trends are noted for the additions of **1**, **4**, and **7** to tetracyanoethylene **42** and dicyanoacetylene **44**, respectively—and in as far as the corresponding experiments have been carried out—to maleic anhydride **43**, perfluoro-2-butyne **45** and dimethyl acetylenedicarboxylate **46**. Only the comparatively unreac-

Table 1. Diels-Alder additions of [2$_n$]cyclophanes in benzene [33].

Dienophile \ Diene	 1	 4	 7	 8	 9	 11
4-phenyl-1,2,4-triazoline-3,5-dione **41**	20 °C, 138 h, 99% (1 : 2-adduct)	20 °C, 3 h, 79% (1 : 1-adduct); 20 °C, 24 h, 65% (1 : 2 adduct)	20 °C, s, 100% (1 : 2 adduct)	20 °C, 24 h, no reaction	20 °C, 24 h, no reaction	—
tetracyanoethylene **42**	100 °C, 15 h, π-complex; 165 °C (in toluene), 13 h, no reaction	20 °C, 20 h, 59% (1 : 1 adduct) + 26% π-complex	20 °C, s, 100% (1 : 1 adduct) [18, 36]	20 °C, 20 h, π-complex	100 °C, 15 h, π-complex	—
maleic anhydride **43**	180 °C (in toluene) 37 h, no reaction	100 °C, 10 h, 53% (1 : 1 adduct)		100 °C, 16 h, no reaction	100 °C, 17 h, no reaction	
dicyanoacetylene **44**	120 °C, 32% (1 : 1 adduct); 170 °C, 72% (1 : 2 adduct) [34]	20 °C, 14 d, 78% (1 : 1 adduct); 81 °C, 24 h, 30% (1 : 2 adduct)	60 °C, 6 h, 93% (1 : 1 adduct), 70 °C, 2 d, 76% (1 : 2 adduct) [36]	—	—	prolonged heating: no reaction [18a]
perfluoro-2-butyne **45**	—	—	100 °C, 12 h, 66% (1 : 2 adduct) [36]	—	—	—
dimethylacetylene dicarboxylate **46**	no reaction at higher temperature [35]	170 °C, 61% (1 : 1 adduct) [35]	—	—	170 °C, 1 h, no reaction	—
dimethyl maleate **47**	165 °C, 13 h, no reaction	100 °C, 10 h, no reaction	—	—		—

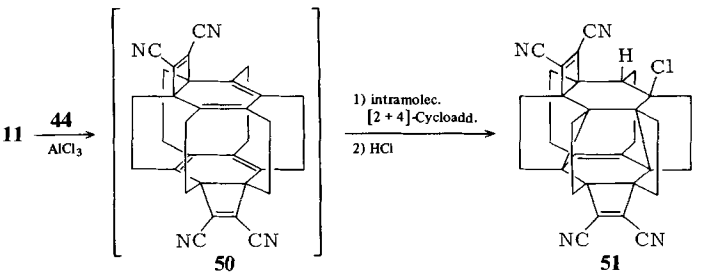
tive dimethyl maleate **47** does not undergo cycloaddition to **1** and **4**. That large ring strain in the educt alone does not suffice to induce a Diels-Alder addition in multibridged cyclophanes, however, is demonstrated by hydrocarbons **8**, **9**, and **11**[18a], none of which reacts with the various dienophiles (Table 1). Apparently in order to participate in a [2+4]-cycloaddition as a diene, a multibridged cyclophane must have a pair of *para*-hydrogen atoms. During the Diels-Alder reaction, which is accompanied by a rehybridization from sp^2 to sp^3, the methylene groups in **8**, **9**, and **11** have to be disposed towards the interior of these molecules, whereas in **1**, **4**, and **7** only hydrogen atoms are relocated. Furthermore, the substitution patterns in **8**, **9**, and **11** lead one to expect a compression of the C—C-bonds in the ethano bridges. The built-up of strain in the σ-framework of the expected Diels-Alder adducts hinders the addition reactions. The only hydrocarbon that does not fit into this scheme is the [2$_5$]cyclophane **10**, which surprisingly reacts with both dicyanoacetylene **44** (60 °C, 3 d, 44%) and perfluoro-2-butyne **45** (100 °C, 7 d, 100%), to afford 1 : 1-adducts[18b].

The important influence of ring-strain in these cycloadditions is impressively demonstrated by cyclophane **7**, which reacts faster than any of the other multibridged systems[36]. As shown by the data in Table 1, **7** initially forms a monoadduct with **44**; however, this is reactive enough to either produce the 2 : 1-product or to form a "mixed" adduct with tetracyanoethylene **42** within a matter of seconds[36]. If, on the other hand, the ring-enlarged, and hence probably less strained, ether **48** is treated with **41** the addition stops at the 1 : 1-stage **49**[17].



48 **49** (100%)

That **44** and superphane **11** do not undergo [2+4]cycloaddition has already been pointed out (Table 1). If, however, these two components are exposed to the catalytic influence of aluminum trichloride, then even at room temperature (3 d, dichloromethane) the polycycle **51** is



produced (40%), whose complicated structure was determined by X-ray crystallography[18a].

To explain the formation of **51** it has been proposed that **11** is first transformed into the 2 : 1 adduct **50** by double [2+2]cycloaddition, that this stabilizes itself by an intramolecular [2+4]cycloaddition, and that the resulting tetraene is trapped in an ionic reaction by the HCl formed during the process to provide the isolated product **51**—a reaction cascade involving three of the most important types of addition reactions.

Summarizing the results presented so far, it can be stated that the Diels-Alder additions of [2$_n$]cyclophanes are controlled by strain effects in both the educt and product molecules. Thus [2.2.2](1,2,4)(1,2,5)cyclophane **26** prepared

from **4** by Lewis-acid catalyzed isomerization (see Section 3.2), and hence is less strained than **4**, does not take up **41** or **42**, even as a π-complex[37]. In this case, the high strain energy of the conceivable cycloadduct most probably hinders the addition. On the other hand, the strain in **1** is just high enough to allow cycloaddition. These arguments are necessarily rather qualitative; however the experimentally determined strain energies of **4**—**11** are presently not available. It would also be desirable to extend the type of dienophiles employed, heteroatom-containing addends being of special interest. One of the few known reactions of this kind involves the sensitized photooxidation of **7**, which leads to the expected *endo*-peroxide[36]. Derivatives like this may be used as starting materials for further oxygenated cyclophanes[38].

4.2. Hydrogenations

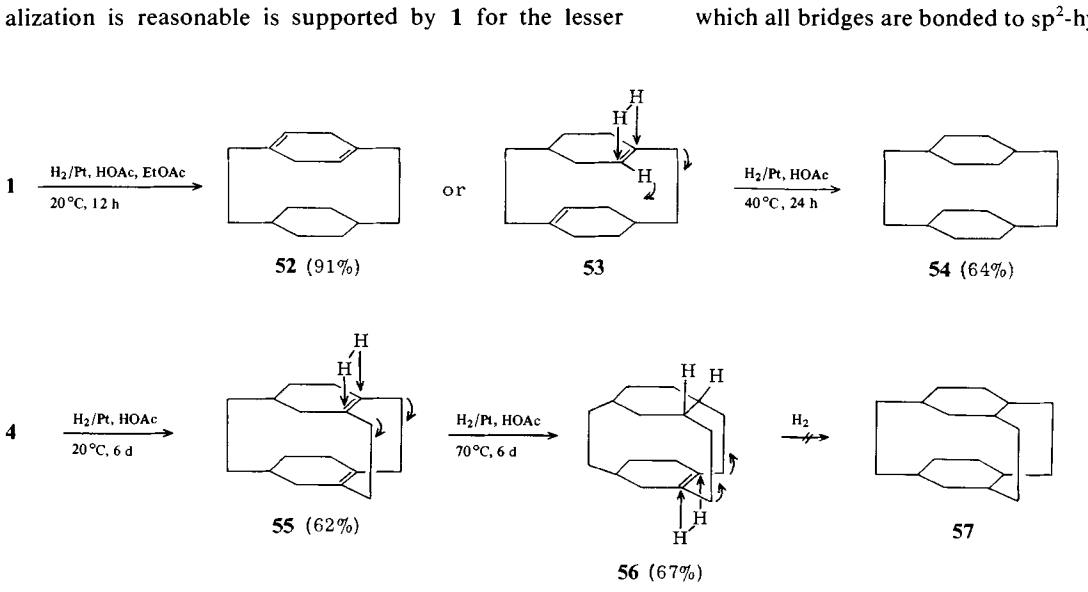
The behavior of [2$_n$]cyclophanes in catalytic hydrogenations may be compared to their Diels-Alder additions in more than one respect. The parent compound **1** is transformed under mild conditions into a diene that either has structure **52** or **53**, whereas slightly more rigorous reaction conditions yield perhydro[2.2]paracyclophane **54**[39]. The incorporation of an additional bridge—as in **4**—is of no immediate consequence: in presence of platinum in glacial acetic acid, four equivalents of hydrogen are added rapidly, and the diene **55** is formed[15a]. Further hydrogenation of **55**, however, requires even more drastic conditions: only after 6 d at 70 °C[15a] or 5 d at room temperature at 5 bar[40] is the monoolefin **56** produced, which is resistant to further hydrogenation under the above conditions.

The low rate of conversion of **55** into **56**, which proceeds considerably more slowly than the hydrogenation of **4** to **55**, can again be attributed to strain effects: the hydrogen necessarily has to attack **55** from the "outside", causing a "compression" of the vicinal ethano bridges and hence increases the strain in the polycycle (bent arrows in **55**). For **56**, rehybridization from sp^2 to sp^3 carbon atoms is opposed by even stronger strain effects, and the perhydro-derivative **57** is therefore not formed. That this rationalization is reasonable is supported by **1** for the lesser bridged cyclophanes, and by **8** (no uptake of H_2 after 7 d at 70 °C and 2.5 bar[22]), **10**[18b], and superphane **11**, which is unreactive towards hydrogen in the presence of Adams' catalyst[18a] for the higher bridged molecules.

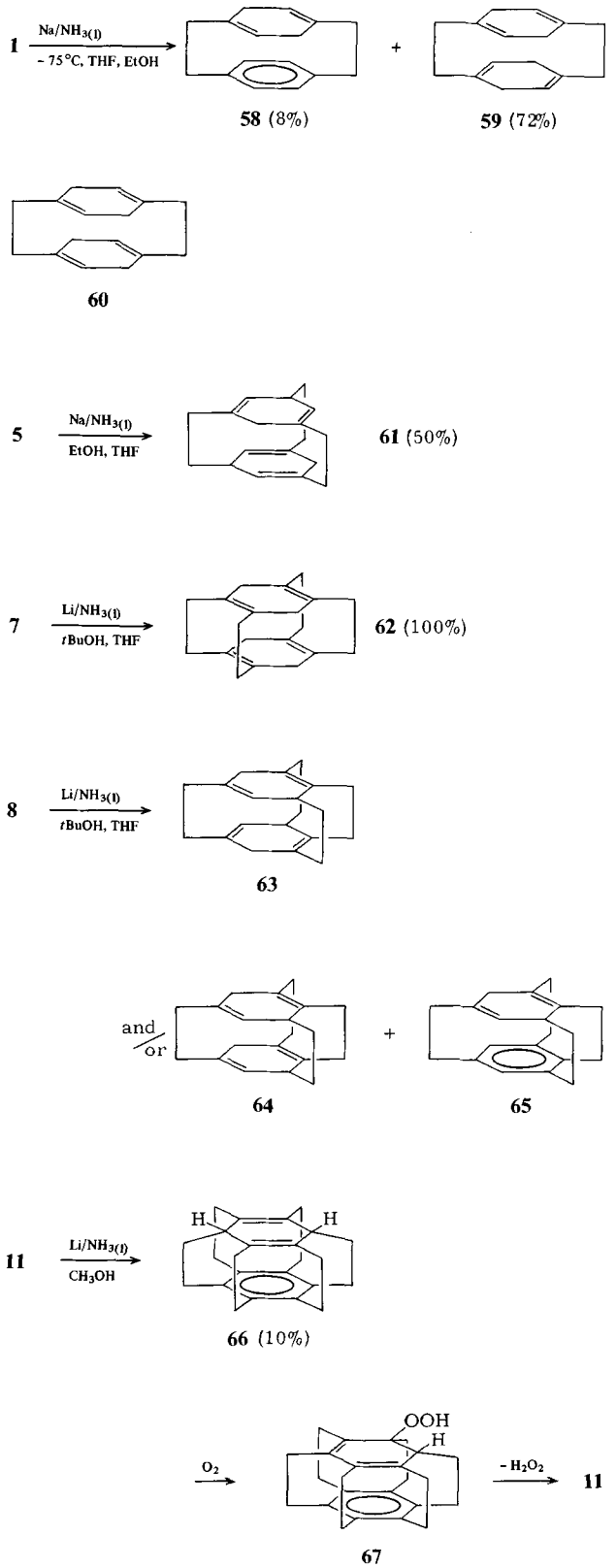
Qualitative indications on the behavior of the benzene rings of [2$_n$]cyclophanes during reduction may also be gathered from Birch reductions, which so far have been carried out with **1**, **5**, **7**, **8**, **10**, and **11** (Scheme 4). This reaction should take place particularly readily, since a substantial reduction in strain is expected for the transformation of non-planar aromatic nuclei into boat-configurated 1,4-cyclohexadiene units.

Under the conditions given in Scheme 4, [2.2]paracyclophane **1**, besides providing small amounts of the dihydro compound **58**, mainly affords the tetrahydro derivative **59**, the "crossed" arrangement of its double bonds being inferred from subsequent reactions and the spectroscopic properties of the products formed[23,41]. Differentiation between **59** and the tetraolefin **60** with "parallel" double bonds, can only be carried out with difficulty using spectroscopic methods alone. Heating **59** to 150—160 °C in a closed system leads to **58**[41a]. The known[42] strong dependence of the product composition in Birch reductions on small variations in the reaction conditions is also observed for **1**; whereas addition of a solution of **1** in tetrahydrofuran (THF) to a refluxing solution/suspension of sodium in liquid ammonia, followed by addition of ethanol yields 4,4'-dimethylbibenzyl **13** in 94% yield[23], slow addition of **1** in tetrahydrofuran/ethanol to a solution of sodium in refluxing ammonia leads quantitatively to **59**[41b]. Birch reduction of the higher homologs of **1** should again be partially governed by the same factors that control the diene reactivity of the [2$_n$]cyclophanes (cf. Section 4.1). Examination of molecular models indicates that the six-ring sp^3-carbon atoms of **59** are strongly tilted "outwards", *i.e.* the cyclohexadiene rings have a boat configuration. An ethano bridge anchored at these positions would probably have to be stretched considerably, causing a severe increase in strain energy in the system.

It is therefore not surprising that in the Birch reduction of **7**, exclusively and quantitatively the energetically more favored tetrahydro[2$_4$](1,2,4,5)cyclophane **62** is formed, in which all bridges are bonded to sp^2-hybridized ring carbon



atoms[36]. The observation that **5** is readily reduced to **61**[24] does not contradict this explanation since a *meta*-arrangement of the bridges, as in substrate **5** and tetraene **61**, tolerates ring-strain more easily. It was hence even more interesting to study the Birch reduction of **8**, a formal hybrid of a [2.2]para- and a [2.2]metacyclophane.



Scheme 4. Birch reduction of [2$_n$]cyclophanes.

Reaction with lithium in liquid ammonia/*tert*-butanol yields a mixture of **63** and/or **64**, and **65**[22]. It is difficult to decide which of the two tetrahydro compounds is present from the spectroscopic evidence—as in the tetrahydro derivative of **1** *(vide supra)*. Steric arguments favor **63**, since sp^3-hybridization of both bridgehead carbon atoms of one ethano bridge (cf. **64**) probably cannot be realized. If the reaction mixture is studied by thin layer chromatography immediately after the reduction has been terminated, **63/64** is found to be practically the only primary product. Hydrocarbon **65** is only present in trace amounts, and substrate **8** has been completely consumed. After purification of the products by column chromatography, however, **65** (6%) and **8** (6%), besides **63/64** (83%) are isolated. The severely strained **63/64** hence begins to rearomatize during work-up at room-temperature; it is stable for several days only at $-20\,^{\circ}C$. The dihydroderivative **65** is somewhat more stable than **63/64**; however, purification by either recrystallization or sublimation fails again, **8** being reisolated.

In its reduction behavior superphane **11** fits neatly into this series: it yields the Birch product **66** (although only in 10% yield) but this rearomatizes rapidly at room temperature to **11**[18a]. Mechanistically this dehydrogenation could proceed as a thermal, symmetry-allowed process as known for other, simple 1,4-cyclohexadiene derivatives[43], or alternatively as an ene-reaction *via* **67** initiated by atmospheric oxygen[18a] and subsequent elimination of H_2O_2. Interestingly enough, hydrocarbon **10** also plays a special role in this reaction: it survives the Birch-reduction unchanged[18b].

The bridge-cleaving hydrogenation of **11** has already been discussed in Section 3.2: Birch reduction of **5** to a dimethyl[2.2]metacyclophane has also been accomplished[24].

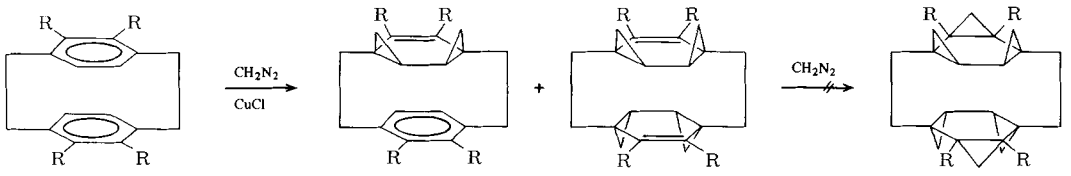
4.3. Various Addition Reactions

Considering the great ease with which some [2$_n$]cyclophanes participate in such typical polyene reactions as the Diels-Alder addition (Section 4.1), it is obvious to submit these hydrocarbons to other classical olefin reactions.

Indeed, the tetraester **68** reacts at room temperature with diazomethane/copper(I) chloride to yield a complex product mixture, from which the methylenation products **69** and **70** could be separated by column chromatography[44].

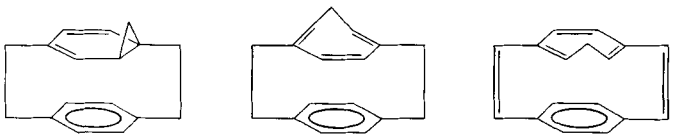
On the other hand, further carbene addition to afford a derivative of the so far unknown *all-cis*-trishomobenzene (*e.g.* **71**) no longer takes place[45]. The electron-withdrawing effect of the methoxycarbonyl groups is not responsible for this inertness, since the tetramethyl[2.2]paracyclophane **72** also yields only bis- **73** and tetra-adduct **74**, respectively[45]. [2.2]Paracyclophane **1** can also be cyclopropanated under the above conditions, providing the norcaradiene **75** in 10% yield, and the ring-enlarged cyclophane **76** in the same yield[46,47].

Surprising in the [2.2]cyclophane series is the observation that [2.2]paracyclophane-1,9-diene is preferentially at-



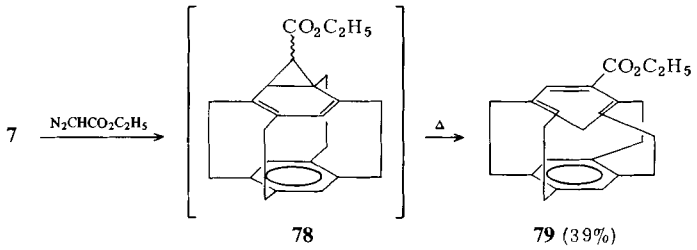
68, R = CO_2CH_3 **69**, R = CO_2CH_3(4%) **70**, R = CO_2CH_3(8%) **71**
72, R = CH_3 **73**, R = CH_3(3%) **74**, R = CH_3(8%)

tacked at one of the benzene rings, hydrocarbon **77** being isolated as the product[47]. As a rule, olefinic double bonds are cyclopropanated more readily than aromatic ones[48].



75 **76** **77**

The norcaradiene derivative, **78**, also ought to be the most likely primary product in the reaction of **7** with ethyl diazoacetate; under the reaction conditions, however, it isomerizes spontaneously to the seven-membered ring system **79**[36].

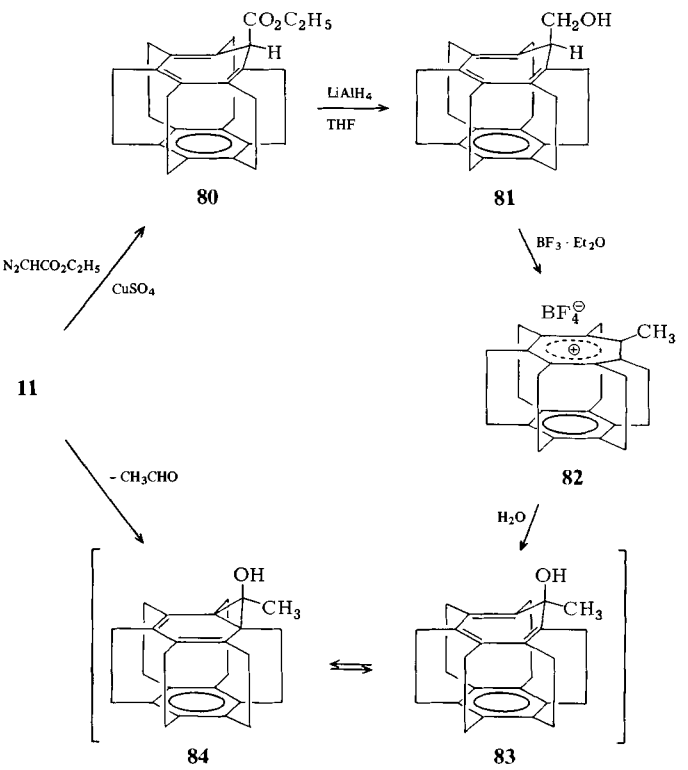


78 **79** (39%)

Tropilidenes like **76**, **77**, and **79** are of interest primarily as starting materials for phane systems in which an uncharged aromatic nucleus, like the benzene ring, is connected to a tropylium ion by ethano bridges and fixed in a stereochemically unambiguous position. Indeed, it has been possible to prepare the simplest molecule of this class of compounds, [2]paracyclo[2](1,4)tropyliophane, from **76** by hydride abstraction, and to study the interaction between the π-systems of its aromatic subunits[46,49]. Recently, a tropyliophane has been obtained from **79**[36]. If the preparative methodology developed in these syntheses is applied to **11**, the "circular process" shown in Scheme 5 results[18a].

As in the case of **7**, addition of ethyl diazoacetate first leads to a tropilidene ester **80**; its reduction with $LiAlH_4$ provides the alcohol **81**, which with boron trifluoride etherate isomerizes (presumably by a hydride shift) to the tropyliophane **82**. When this salt is either recrystallized from methanol/water or allowed to stand exposed to the atmosphere it is reconverted into **11**. This remarkable decomposition could occur *via* alcohol **83**, which after it undergoes valence isomerization to **84** by acetaldehyde cleavage, rearomatizes to **11** (52%)[18a].

Exploratory epoxidation experiments with *m*-chloroperbenzoic acid lead for **1** and **72** to oxidative degradation of the benzene rings, whereas the less electron-rich tetraester **68** yields a bisepoxide in 21% yield[45].

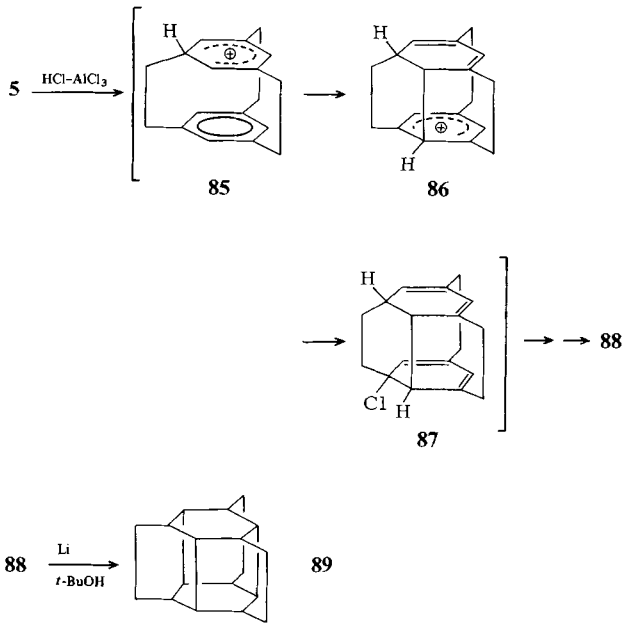


80 **81** **82** **11** **84** **83**

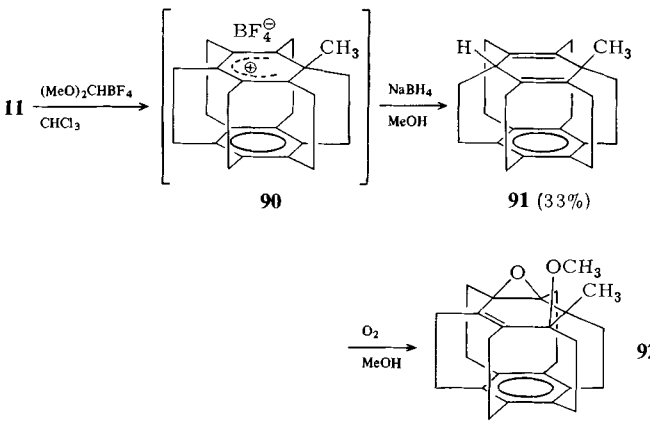
Scheme 5. Preparation and properties of a tropylium system derived from **11**.

Ionic additions to the benzene rings of the multibridged cyclophanes would certainly hint at a reduced aromatic character of these molecules, and in fact there are several reports in the literature describing this type of reaction: for example, **5** is transformed into a complex product mixture of composition $C_{18}H_{18}\cdot H_xCl_{6-x}$ (**88**) when treated with $HCl/AlCl_3$ in CH_2Cl_2 for 10 min at 0 °C. The separation and identification of the different chlorides was unsuccessful; however, **88** could be reduced to a homogeneous hydrocarbon $C_{18}H_{24}$, which—according to spectral data—has the cage structure **89**[24].

A plausible precursor for **88** is the HCl-adduct **87**, formed from **5** *via* the σ-complexes **85** and **86**. Monochloride **87** is well-suited for a multiple repetition of this ionic addition.



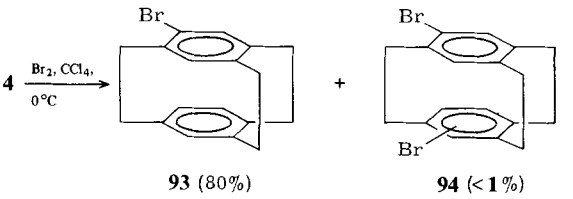
In another ionic process, **11** is alkylated with the Meerwein reagent dimethoxymethylium tetrafluoroborate to give the cation **90**, which may be intercepted by hydride ions to afford **91**. When this hydrocarbon is recrystallized from methanol it reacts to furnish epoxide **92** or a positional isomer thereof[18a].



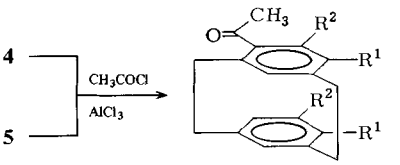
Polymethylated [2.2]paracyclophanes also react very rapidly with HCl to yield various chlorides, of as yet unknown structures[50].

4.4. Reactions in which the Benzene Rings are Conserved

The method of choice for the preparation of simple derivatives of [2.2]paracyclophane **1** is electrophilic aromatic substitution. Bromination, Friedel-Crafts acylation, nitration, and other reactions have all been reported[9] and are normally carried out under conditions characteristic for this type of substitution reaction. It can hence be assumed that in the majority of cases the standard reaction mechanism is also followed. However, precise mechanistic studies are rare and are, furthermore, primarily concerned with the mode of secondary- and polysubstitutions, and not with the primary process. *A priori* there is no reason to preclude substitutions that take place by an addition-elimination mechanism.



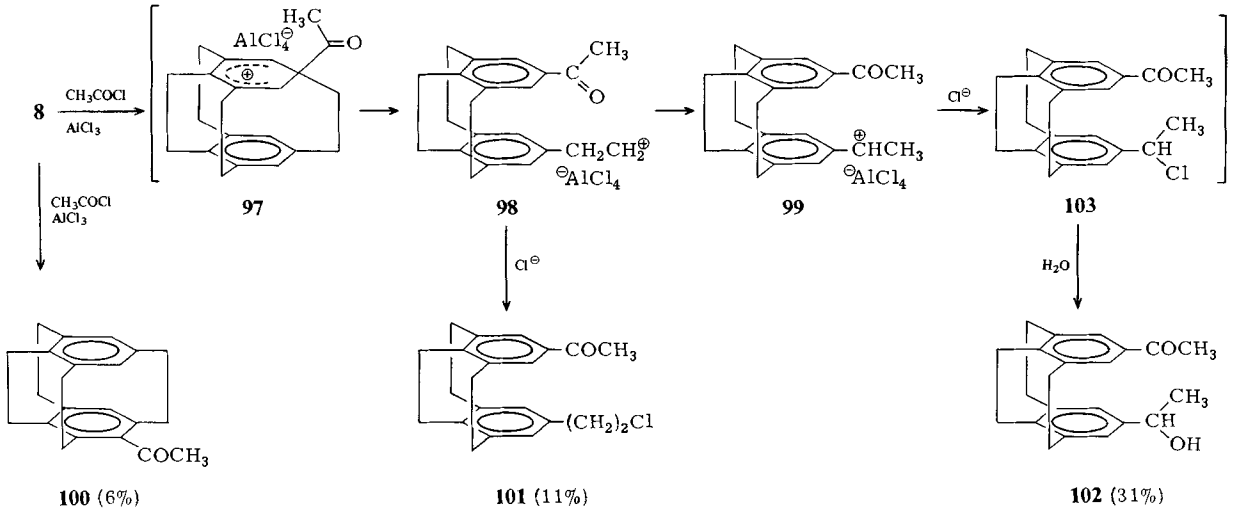
Bromination of the multibridged phane **4** provides the expected monobromide **93** as well as traces of the dibromide **94**[15a]. **4** is more reactive than **1**, and the fourfold bridged phane **8** cannot compete with **4** either: under the above conditions it does not react with bromine, and the addition of iodine or an increase of the reaction time is at first also of no consequence. Only when the reaction times become very long (16 h) does the bromine solution decolorize; however, from the resulting multi-product mixture, no monosubstituted derivative could be isolated[22]. Possibly addition of the electrophile occurs, as in the case of **5** in the presence of HCl.



95, R^1–R^1 = CH_2CH_2, R^2 = H(79%)
96, R^2–R^2 = CH_2CH_2, R^1 = H(59%)

Friedel-Crafts acylation of **4** and its isomer **5** proceeds as expected to form **95** and **96**, respectively[15]. The methyl ketones **95** and **96** do not undergo further acylation. The (1,2,3,5)cyclophane **8** provides the ketone **100** upon acylation, but only in low yield. The main products—besides reisolated **8** (16%)—are the two (1,2,3)cyclophanes **101** and **102**, respectively (Scheme 6)[22]. The formation of these two ketones requires the breaking of an ethano bridge between the benzene ring and a methylene group, and it seems reasonable to propose an *ipso*-substitution mechanism for this process[51]. The initial intermediate could hence be the σ-complex **97**, which removes part of its strain by isomerizing to the primary carbenium ion **98**. This, in turn, is either intercepted by chloride ions (formation of **101**) or stabilized by hydrogen migration to form the secondary cation **99**. Reaction of this species with chloride ions, however, leads to **103**, a secondary and benzylic halogen-derivative that is hydrolyzed to alcohol **102** during work-up.

Formylation after *Rieche*[52] (Cl_2CHOCH_3, $TiCl_4$, CH_2Cl_2, 0 °C) converts **8** in excellent yield (94%) into the expected aldehyde **104**, whereas nitration (fuming nitric acid, glacial acetic acid, 70 °C, 2 min) yields only traces of the nitro compound **105**[22].



Scheme 6. *Ipso*-substitution of [2$_4$](1,2,3,5)cyclophane **8**.

Both bromination (Br_2/iron) and Rieche formylation transform [2$_5$](1,2,3,4,5)cyclophane **10** into the expected monosubstitution products in excellent yields[18b].

5. Concluding Remarks

Although the homologous series of [2$_n$]cyclophanes with parallel ethano bridges has only been known for about two years[12], many results already exist on the chemical behavior of this new class arenes. Compared to classical monocyclic arenes their most distinct chemical property is the ease with which several of these phane systems participate in addition reactions. This behavior has been termed cyclohexatrienoid[33,35].

At most, however, this term describes the formal course of these additions. A "real" cyclohexatriene must show alternating single and double bonds—but just this property is not observed in any of the [2$_n$]cyclophanes that have been investigated by X-ray structural analysis[25-30].

The chemical reactions of **4**—**11**, as already mentioned in the text, need to be studied in greater detail. This is particularly true of photo-processes, which have been neglected so far. To put the mechanistic discussions on a quantitative level it would be desirable to compare the rates for the above reactions with those for their corresponding "halves", *i.e.* the various methylbenzenes. The direct observation of several reactive intermediates, like the various σ-complexes, would also be of mechanistic importance.

A *conditio sine qua non* for these and other investigations is synthetic methods that provide larger amounts (*i.e.* gram quantities) of the different [2$_n$]cyclophanes. In closing it should be mentioned that several of the synthetic pathways leading to the new hydrocarbons do not yet fulfill this all-decisive condition.

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4-Oxo-2-cyclopentenyl Acetate—A Synthetic Intermediate[1]

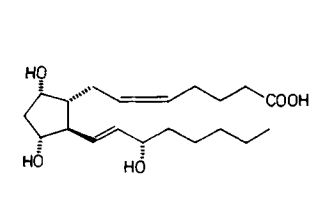
By Michael Harre, Peter Raddatz, Rainer Walenta, and Ekkehard Winterfeldt*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

The present day importance of cyclopentenone derivatives in preparative organic chemistry and especially in natural product chemistry is demonstrated by the stereoselective synthesis of substituted and annelated cyclopentanone derivatives. It has been found that 4-oxo-2-cyclopentenyl acetate ("4-acetoxy-2-cyclopenten-1-one") can be used in many reactions as a substitute for cyclopentadienone, which is itself too unstable to be isolated. A large variety of polyfunctionalized cyclopentanone derivatives, as well as carbocyclic and heterocyclic annelation products, can thus be obtained in a simple way. Various stereoselective transformations of the adducts so formed are presented, using the total synthesis of brefeldin A—a typical natural product of this series—as example. Several methods for the synthesis of 4-oxo-2-cyclopentenyl acetate are outlined and, in addition, the more important methods for the enantioselective synthesis of other 4-substituted 2-cyclopenten-1-ones are discussed.

1. From Prostaglandin to Dodecahedrane—Cyclopentanes

The chemistry of the cyclopentenes, cyclopentanones and cyclopentenones has developed with increasing rapidity in the last twenty years. One of the major reasons for this has been the search for synthetic routes to the prostaglandins (*e.g.* $PFG_{2\alpha}$ **1**[2]), prostacyclins (*e.g.* PGJ_2 **2**[3]), and thromboxanes (*e.g.* A_2 **3**[4]), and to the macrolide antibiotic brefeldin A **4**[5], which exhibits some of the structural features of **1**—**3**.



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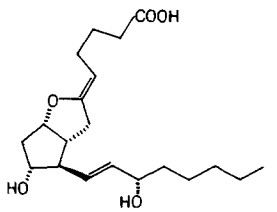

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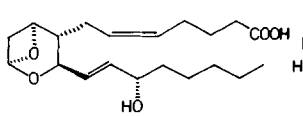

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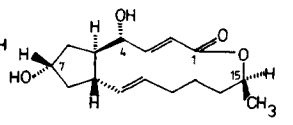

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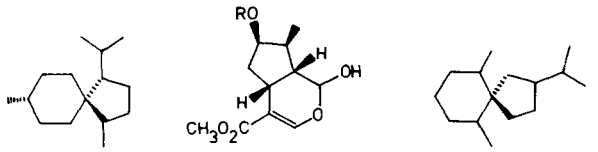
Additional impetus was given to this development through the interest in cyclopentanoid terpenes, *i.e.* the acoranes **5**[6], iridoids **6**[7], spirovetivanes **7**[8], hydroazulenes **8**[9], and, particularly, the pseudoguajanolides[10] and steroids **9**, as well as in the total synthesis of hirsutic acid **10**[11], pentalenolactone **11**[12], isocomene **12**[13], and modheptene[14].



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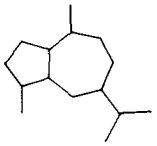

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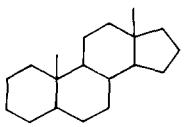

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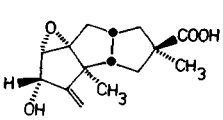

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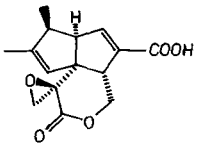

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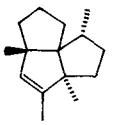

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Finally, substances such as pentalene **13**[15,16], triquinacene **14**[16] and the tetraquinanes, pentaquinanes and hexaquinanes leading to dodecahedrane **15**[16], which have been studied primarily because of their theoretical and stereochemical interest, have also greatly enriched our understanding of the chemistry of the cyclopentanes.

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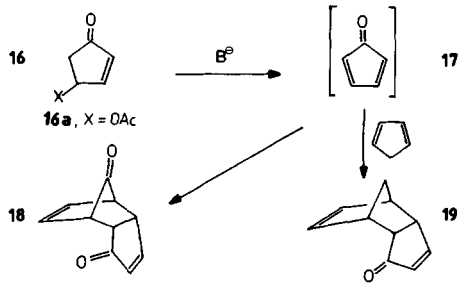
Many important intermediates have been prepared, interesting synthetic strategies for the synthesis of cyclopentanoid compounds have been developed, and many of the idiosyncratic and characteristic properties of the cyclopentane system have been revealed.

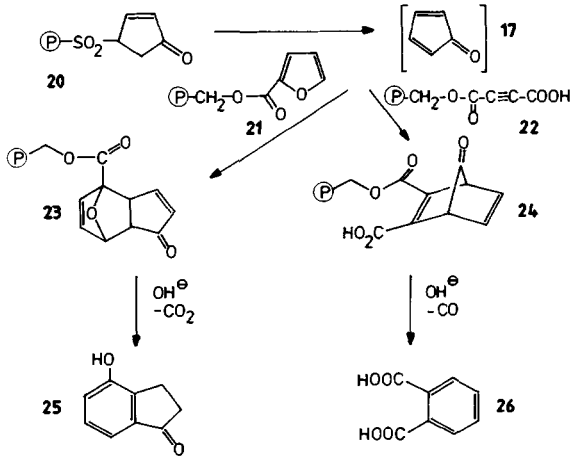
2. The Starting Material of Choice: Reactive but Tamable, Versatile but Docile

Our interest was especially aroused by the promising reactivity of substituted cyclopentanones of type **16** containing a good leaving group. These substances tend to undergo rapid elimination with formation of the unstable and highly reactive cyclopentadienone **17**[17], which, under normal conditions, generally dimerizes to **18** and cannot be isolated or manipulated in the monomeric state.

As early as 1964 *DePuy et al.*[18] were able to prevent this dimerization by addition of cyclopentadiene, which reacts



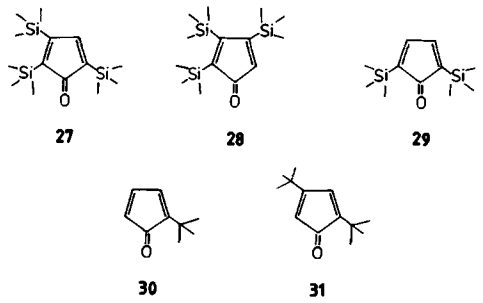
with cyclopentadienone as dienophile to give the cycloadduct **19**. In this reaction the dienone **17** thus functions exclusively as 2π component, whereas in the very fast dimerization, which excludes detection of the monomer, it obviously reacts both as dienophile as well as diene. Last year, all lingering doubts as to the actual existence of the monomer in solution were removed by a so-called three-phase test[19] (P in a circle signifies polymer).



The solid phase bound cyclopentadienone precursor **20** generates cyclopentadienone **17**, which then reacts with either the 2π-partner **22** or the 4π-partner **21**, which are also bound to the solid phase. Subsequent hydrolysis releases the cycloadducts **24** and **23**, respectively, from the polymer, and their stable end products **26** and **25** can be isolated.

The generation of the dienone **17** by pyrolysis or flash pyrolysis in the gas phase has been reported by various groups[20]; *Maier et al.*[21] recently succeeded in carrying out the first matrix isolation of this substance, in the vacuum discharge pyrolysis of the acetate **16a**. It was in connection with this experiment that *Maier et al.* also synthesized the first cyclopentadienone equivalent that proved to be stable at room temperature: The 2,3,5-trisilylated compound **27** can be handled as the monomer at room temperature, whereas the 2,3,4-isomer **28** dimerizes completely within a week. A disilylated analogue **29** has been described by *Vollhardt et al.*[22]; however, like **28**, this compound dimerizes at room temperature.

Even earlier, it had been demonstrated on several occasions that multiple substitution dramatically changes the behavior of the dienone **17**[23]. As long ago as 1966, *Garbisch et al.*[24] prepared the rapidly dimerizing *tert*-butyl derivative **30** by elimination, as well as the di-*tert*-butyl



compound **31**, which also has a short half-life at room temperature.

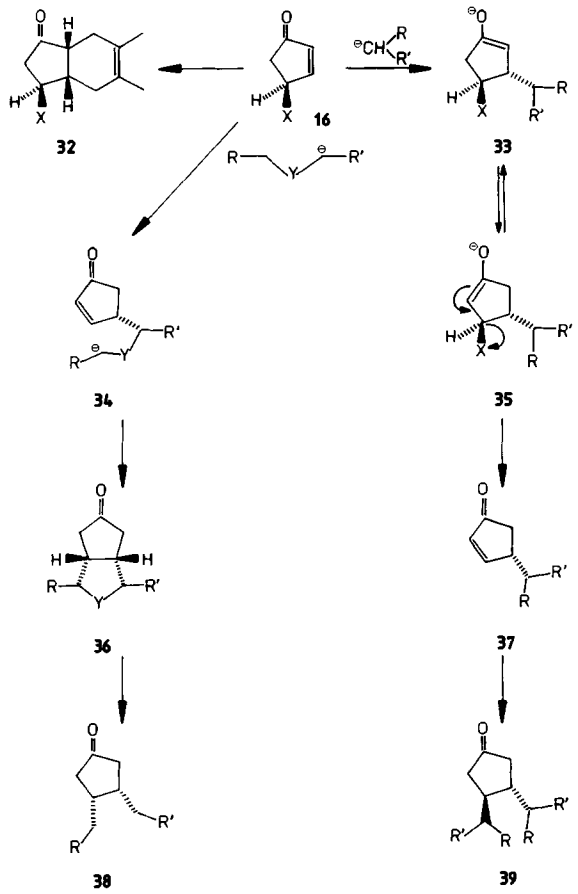
For the preparation of **31** *DeSelms* and *Schleigh*[25] carried out the *o*-quinone decarbonylation reaction described by *DeJong et al.*[26] and by *Chapman et al.*[27] on 3,5-di-*tert*-butyl-*o*-benzoquinone and were able to confirm that the product had a great tendency to dimerize[24].

The special electronic structure of compounds of this type suggested the *a priori* possibility that the high reactivity and tendency to dimerize were a result of the presence of the intact carbonyl group; thus, it appeared purposeful to seek a remedy in carbonyl derivatives having an sp^3-hybridized center. The relevant ketals[28], however, were also found to dimerize very rapidly, even more rapidly than the parent cyclopentadiene itself.

In view of these findings it seemed unlikely that cyclopentadienone **17** itself could ever be used as a synthon, so we searched for a synthetic equivalent designed to generate reaction products expected from **17** without the disadvantages of the highly reactive 4π-system.

It is one of the intellectually stimulating features of goal oriented total synthesis that the utility of a synthon is not just dependent upon its structural characteristics but on its inherent synthetic potential, *i.e.* upon the products into which it can be converted. Why try to experiment with an awkward and reactive substance when it is possible to find a stable, well behaved and reliable substitute? It seemed possible, for instance, that the acetate **16a** might be a substitute for cyclopentadienone **17**, since Michael additions, for example, should yield the same products from **16a** as from **17** (Scheme 1).

If Michael donors with CH-activities higher than that of the ring CH_2-group of the cyclopentenone derivative **16** are used, Michael addition will lead to formation of the enolate **33** without interference by transprotonation and subsequent elimination and dimerization. Under suitable reaction conditions **33** should be in transprotonation equilibrium with **35**, from which **37**—a compound which can be regarded as the mono-Michael adduct of cyclopentadienone—is formed by elimination. A further addition would be *trans*-directed, thus yielding a *trans*-disubstituted cyclopentanone such as **39**. If a bidentate donor having a short linkage chain Y is used, then *cis*-addition *via* **34** to give **36** is to be expected. If Y were designed to be preferentially cleaved, then this would also open up access to *cis*-disubstituted cyclopentanones such as **38**. It should also be possible to utilize **16** as a dienophile and to form products of the type **32**. Owing to its structure, only the role of 4π-reagent remains impossible for **16**.



Scheme 1.

The applicability of the different Michael donors, which depends on the electronic properties and bulkiness of the acceptors R and R', the influence of the chain length of Y on the configuration of the annelated ring system, and the method of bond cleavage at Y, had to be clarified in detail.

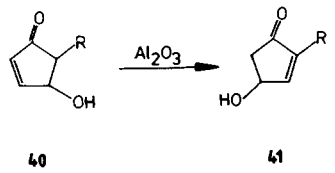
3. Enantiomer-Selective Preparation of the Intermediate

Fortunately, in contrast to cyclopentadienones, compounds of type **16** have the added advantage that they are accessible in a variety of ways and in adequate quantities, and, at the same time, exhibit the stability desirable for a starting material. A number of possible routes which should enable preparative access to 1,3-bifunctionalized cyclopentanes and cyclopentenes are listed in Table 1.

The alcohols and esters thus obtained can be used either directly or, after partial hydrolysis, esterification, or etherification, they can be oxidized to the cyclopentenones.

Table 2 lists the routes leading directly to ketones of type **16**.

It is also worth mentioning that compounds of type **40**, which can be synthesized directly from furans, can be easily isomerized to **41**, thus broadening the range of possibilities. This isomerization to the more highly substituted olefin can also be readily carried out in the absence of a hydroxyl group.



40 41

Table 1. Examples of the synthesis of 1,3-bifunctionalized cyclopentanes and cyclopentenes.

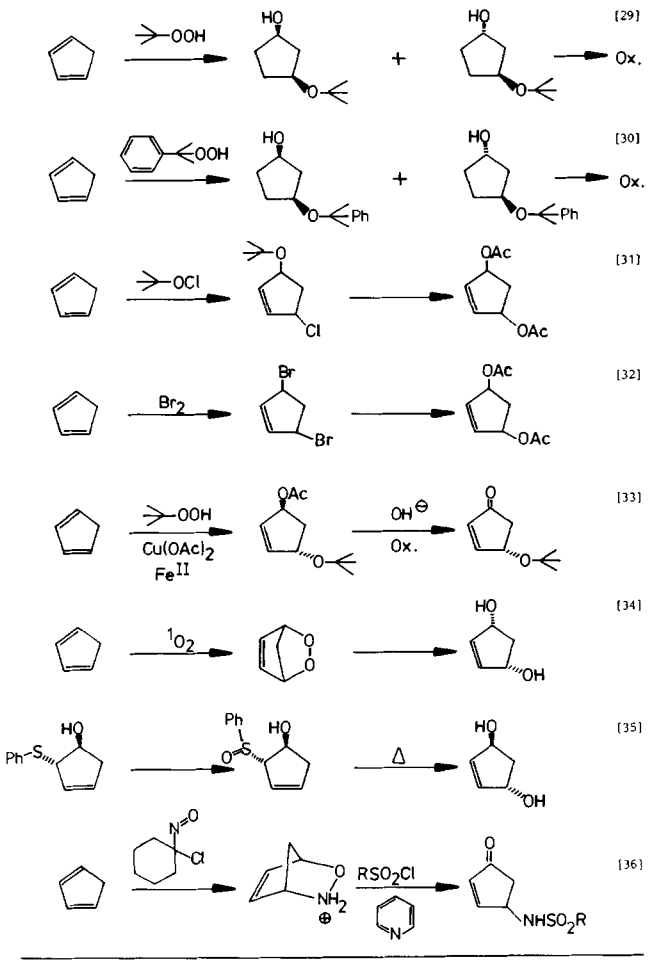
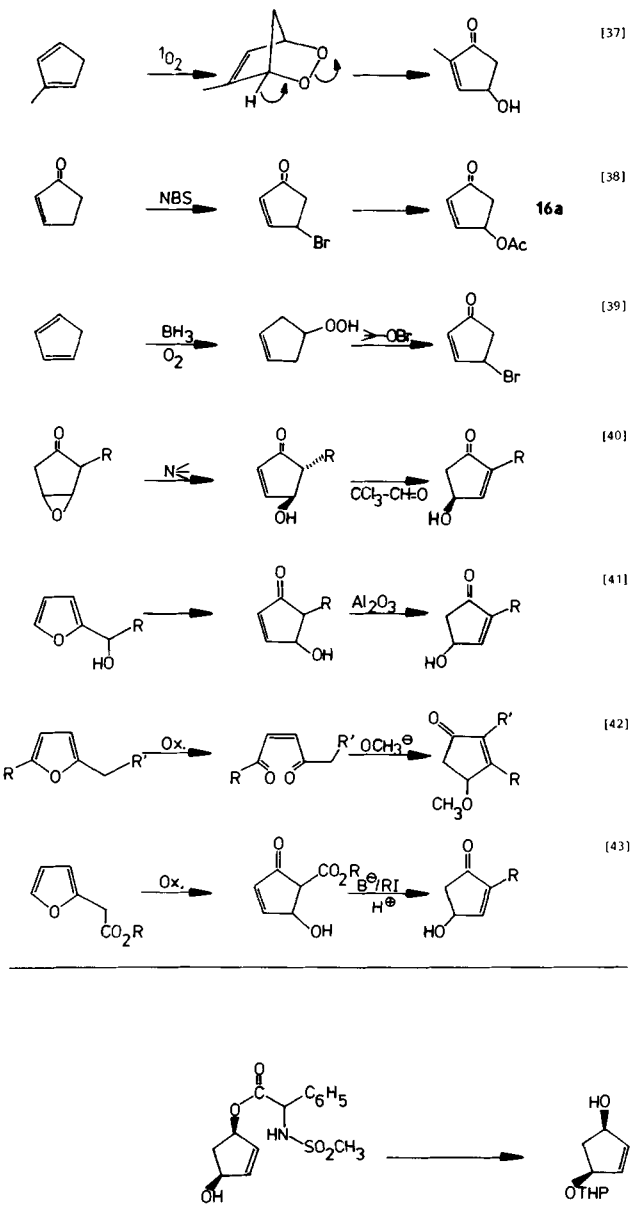


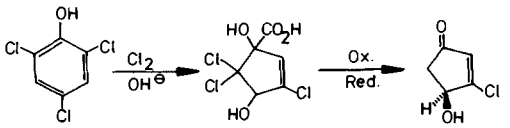
Table 2. Examples of the synthesis of bifunctionalized cyclopentenones of type **16**. NBS = *N*-bromosuccinimide.



Scheme 2. Reaction sequence: 1) Diastereomerization, 2) reaction with dihydropyran, 3) alkaline hydrolysis (THP = tetrahydropyranyl).

Considering the numerous interesting classes of substances which can be synthesized with the aid of these substituted cyclopentenones it is not surprising that concerted efforts have also been made at preparing the pure enantiomers. After *Fischli et al.*[44] had introduced the concept of economic enantioselective synthesis, it was logical to apply it also to cyclopentene derivatives[45] (Scheme 2). Separation of the diastereoisomeric sulphonamides is not an easy task, and carrying out the reaction sequence in our laboratories gave cause for reflection on its utility on a larger scale.

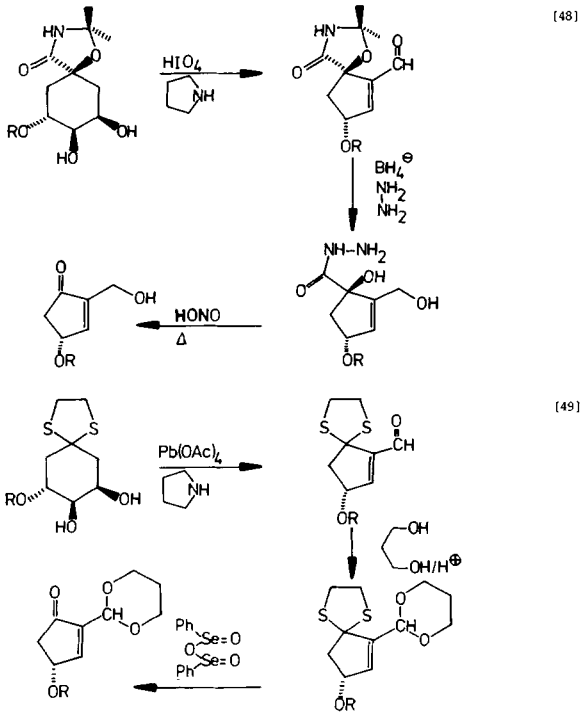
The method starting from trichlorophenol, as described by *Gill, Rickards et al.*[46] (Scheme 3), is also not unproblematical. One stage of the process is the separation of a α-hydroxycarboxylic acid racemate obtained by ring contraction of the chlorophenol. Resort to this process revealed it as being far from ideally suited for large-scale preparation: here also there was much left to be desired for the "production" of starting material.—Since the halogen atoms at the sp^3 hybridized center can be removed by selective reduction, an intermediate vinylogous acid chloride can be obtained, which can easily be converted into a substituted hydroxycyclopentenone[47].



Scheme 3.

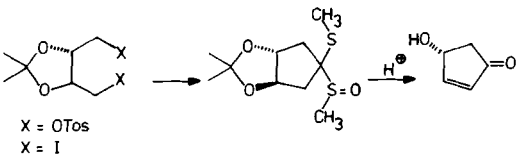
Substituted chiral alkoxycyclopentenones of this kind have also been prepared *via* two routes[48,49] from the chiral pool (quinic acid), without the need for resolution (Scheme

4). In the case of the second method it is remarkable that the configuration of the decisive chiral center is not changed at the unsaturated aldehyde stage and also that the aldehyde as well as the corresponding acetal can be obtained in good optical yield.



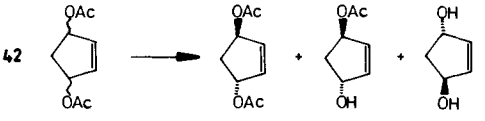
Scheme 4.

The method developed by *Ogura et al.*[50] also makes use of the chiral pool. The commercially available ditosylate obtained from D-tartaric acid is converted *via* the diiodide and alkylation into the thioketal monosulfoxide, which on acid hydrolysis affords the chiral hydroxycyclopentenone (Scheme 5).



Scheme 5.

The possibility of hydrolysis with bakers' yeast[51] was studied on a stereoisomeric mixture of **42**. The chiral *trans*-monoacetate can be isolated from the resulting mixture of compounds and oxidized to **16a**.

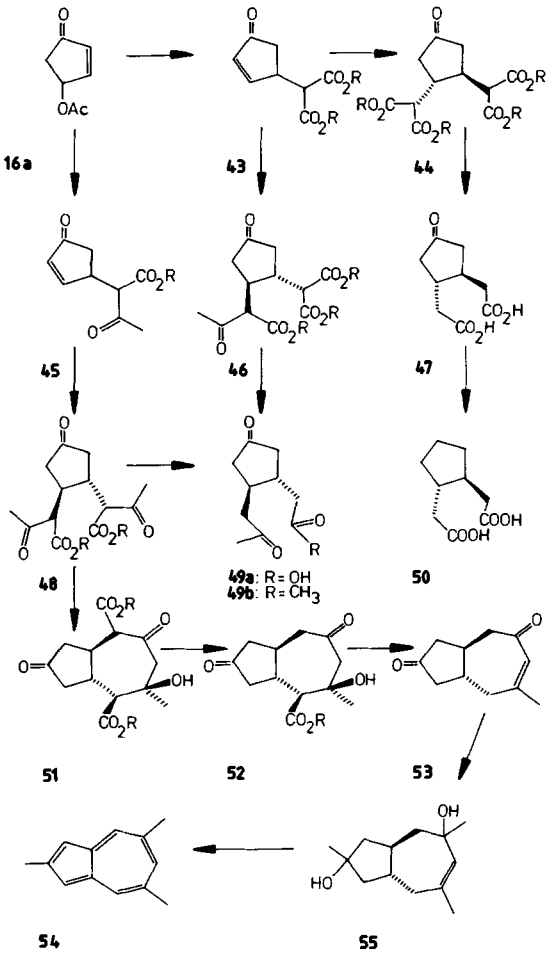


Without wishing to denigrate in any way the advances made in the field of enantioselective synthesis, experimental studies of the methods available up to now have, nevertheless, revealed the need for improvement, especially when it comes to scaling them up.

4. The Importance of Choosing the Correct Leaving Group

Whatever preparative gaps may still have to be closed in the case of the chiral starting material, the desired cyclopentenones are widely accessible using the methods outlined in Tables 1 and 2, and the problem now is which leaving group X best fulfills the requirements of Scheme 1. This is not a trivial question. A critical analysis of the scheme reveals that the margin of safety is small, and that there are many pitfalls to be avoided. If a very good leaving group is employed then there is a danger of premature elimination before the Michael addition has taken place, leading to the formation of the cyclopentadienone, which would then dimerize. Even if, against all likelihood, the high donor concentration made the Michael addition competitive with the dimerization, then the achiral nature of this intermediate would vitiate the effect of any prior chiral synthesis. This danger is also present if X itself possesses acceptor properties, for the increased acidity at the chiral center would lead to a rapid racemization in alkaline media. Too weak a leaving group X, on the other hand, would lead to various difficulties with the primary enolate anion. Since the charged group could not be ejected rapidly there would be the possibility of secondary reactions, of undesired transprotonation, and of an unfavorable addition equilibrium.

Preliminary trials using acetoacetic ester and malonic ester as donors quickly indicated that 4-oxo-2-cyclopentenyl



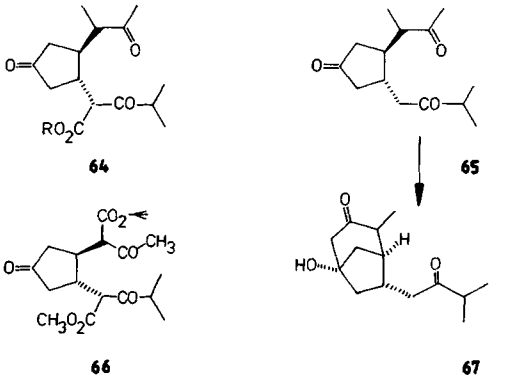
acetate **16a** is a suitable starting material[52]. Monoadducts (**43**, **45**) and bisadducts (**44**, **46**, and **48**) can be generated from malonic and acetoacetic esters. **44**, $R=CH_3$, could be shown by decarboxylation and reduction to **50** to have a *trans*-configuration, while **48**, $R=CH_3$, rapidly underwent cyclization to give the hydroazulene **51**.

Stepwise decarboxylation and dehydration of **51** furnished the unsaturated ketone **53**, an interesting intermediate product in this series which can easily be transformed by reaction with methyllithium and dehydration into trimethylazulene **54** – a further proof of the hydroazulene structure.

5. The Correct Leaving Group is not Everything!

Longer chain β-keto esters can also add to cyclopentenone derivatives **16**, to give **56**[53], from which the triketones **57** can be prepared; substituted malonic esters can also be added, followed by β-keto esters, so that, *e.g.*, the triester **58a** can be prepared and then decarboxylated in good yield to **58b**. However, the limits of the method also become apparent in this study; thus, **58a** cannot be synthesized by reversing the order of the nucleophiles. If valerylacetic ester is used in the first stage it gives **59** in 65% yield, but attempts to add the dimethyl ester of *n*-butylmalonic acid to **59** were unsuccessful. Attempts to force the second addition quickly exposed the weaknesses of this method. The two main weaknesses are a possible retro-Michael addition with dimerization of the cyclopentadienone so produced, and the great tendency of compounds of type **59** to isomerize to stable more highly substituted olefins. Thus, the range of applicability of the reaction is drastically narrowed.

These difficulties also occur on addition of substituted or branched acetoacetic esters. **60** is thermally converted into **61**, and **62**, which is formed in quantitative yield on treatment of **60** with trifluoroacetic acid, smoothly isomerizes to **63** on distillation, if all traces of acid are not carefully removed beforehand[54]. This behavior of cyclopentenones has, in principle, been known for some time, but fortunately it is unimportant for the second addition since no acid is used here. At this stage the retro-Michael reaction is a much more serious handicap, for it leads to undesired side-reactions during the treatment with base that is necessary in the case of hydroazulene cyclization.

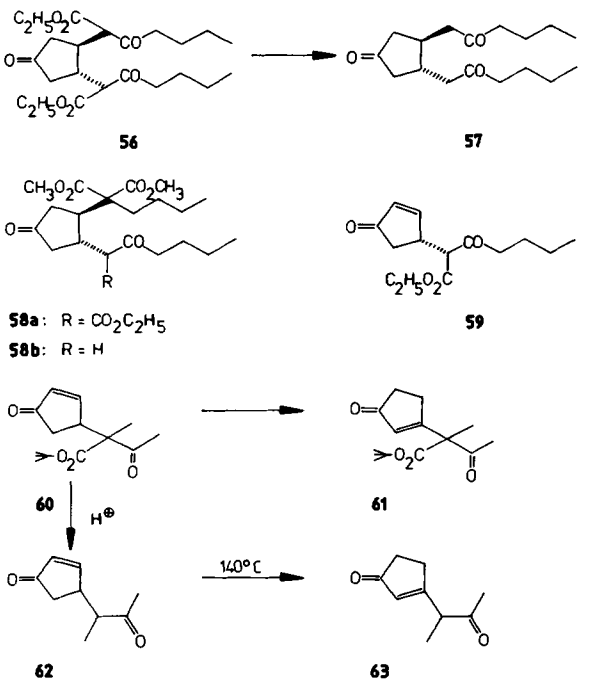


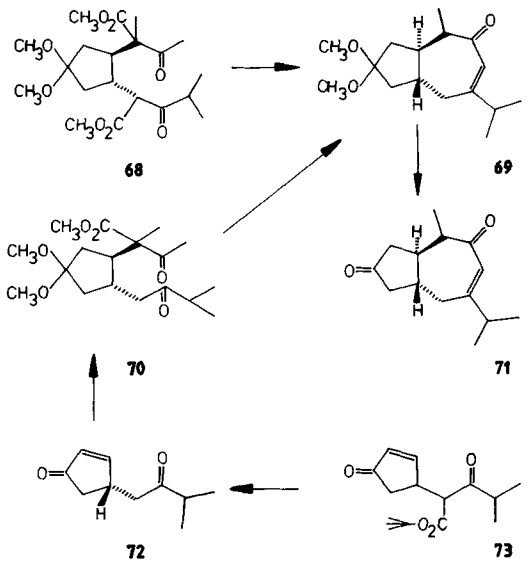
64 **65** **66** **67**

Thus, for example, **64** is accessible in good yield, but it is not possible to cyclize it to the hydroazulene. If **64** is decarboxylated to **65**, cyclization occurs even under very mildly basic conditions. However, the product can, on the basis of spectroscopic evidence (disappearance of the five-membered ring carbonyl band) be assigned the bicyclic diketone structure **67**[55]. Attempts to cyclize β-ketoester Michael adducts of general type **66** to hydroazulenes are also bedevilled by reverse reactions. It is, however, of special importance to find a reliable method for cyclization of these hydroazulene precursors having the typical terpenoid substitution pattern seen in so many natural products. The results obtained up to now suggest that it might be useful to ketalize the keto group in the five-membered ring prior to cyclization of the bisadducts **66** or **68**.

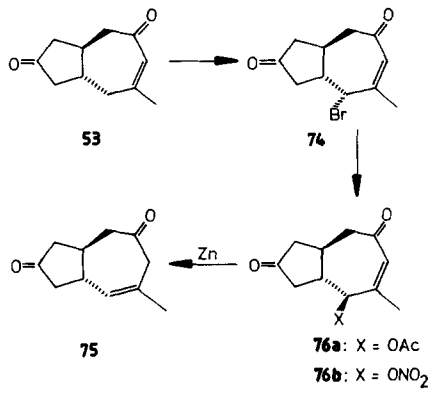
6. Cyclizations

The ketalization suggested above—easily performed with methanol/methyl orthoformate under conditions of proton catalysis—succeeds miraculously. Cyclization and decarboxylation to **69** take place without difficulty, and subsequent deprotection yields the desired diketone **71**[54]. The overall yield can be improved by using the *tert*-butyl ester **73**, which can be transformed into the monoadduct **72** by mild decarboxylation and careful distillation without isomerization. Second addition and ketalization, which take place with excellent selectivity in spite of the presence of three ketone groups, yield the cyclizable intermediate **70**, which can be transformed in high yield into **69** and **71**. Analysis of the product mixture after removing the ketal shows that **71** is always accompanied by a small quantity of the corresponding deconjugated ketone. Such a deconjugation can be achieved in high yield by reduction of γ-substituted derivatives. Investigations of this type have been made using a simple model **53**. Reaction of **53** with *N*-bromosuccinimide leads with high regio- and stereose-





lectivity to the bromoketone **74**[56]. Nucleophilic substitution yields the acetate **76a** or the nitrate **76b**, which upon reduction with zinc smoothly gave rise to the β,γ-unsaturated ketone **75**.

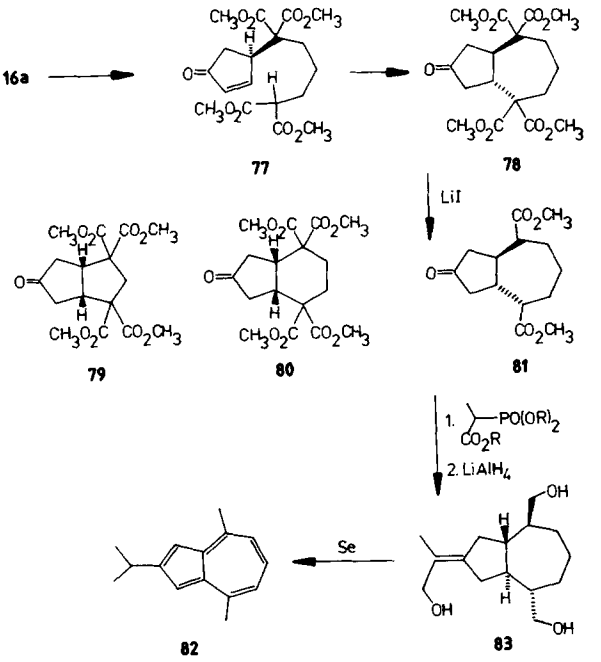


7. Annelation

As can be seen from Scheme 1, annelation with double donors is possible; the hydropentalene- and hydroindene-derivatives **79** and **80**, as well as hydroazulenes **78** can be formed. This stimulated an investigation of the stereochemistry of the reaction as a function of the length of the chain Y, the configuration being determined from NMR data of the particularly easily prepared dimethyl ketals[57]. While **79** and **80** are expectedly *cis*-annelated, *trans*-annelation occurs on formation of hydroazulenes **78** and **81**. The fact that the dimethyl ketals of **79** and **80** show very different signals, as can be expected for a *cis*-system, while in the case of the dimethyl ketal of **78** the resonances were absolutely identical, is in accord with the configurational assignment.

An intermediate product, namely **77**, could only be isolated in the case of **78**. In the case of **79** and **80**, on the other hand, the cyclization takes place immediately after addition; monocyclic addition products could not be detected.

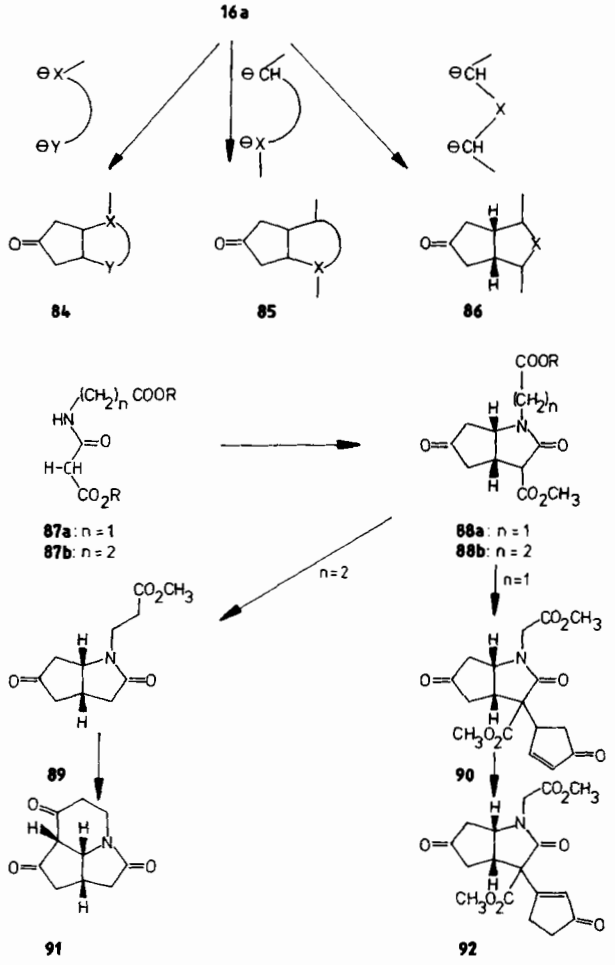
The diester **81** obtainable from **78** by nucleophilic ester cleavage has structural features that make a simple synthesis of vetivazulene **82** possible; it can be transformed by olefination and aluminate reduction into the triol **83**, which, on treatment with selenium, yields vetivazulene.



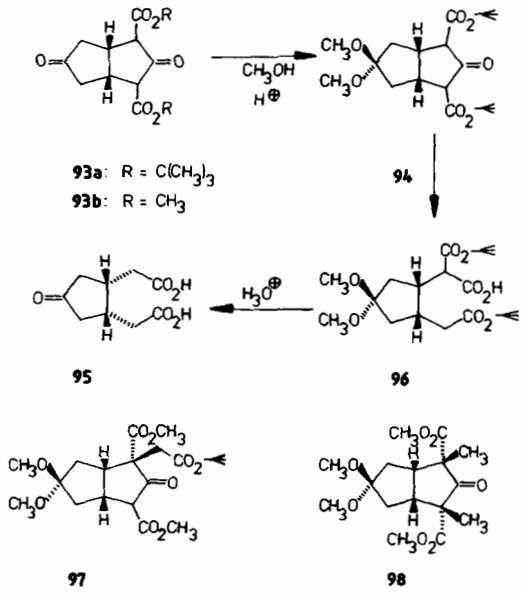
Annelations of this type can, in principle, be carried out with heteroatoms where either both donor centers, as in **84**, are heteroatoms, or, as in **85**, only one is a heteroatom and the other a carbanion. The incorporation of an heteroatom into the chain joining the two donors is another a possibility. In this case any additional carbon acidity that may be conferred by the heteroatom could be of synthetic value, while, additionally, such a center X could be a point of cleavage and lead, *via* intermediates of type **86**, to *cis*-disubstituted compounds. An example of the mixed variant is the addition of malonamides, which leads to compounds of the type **85**[57].

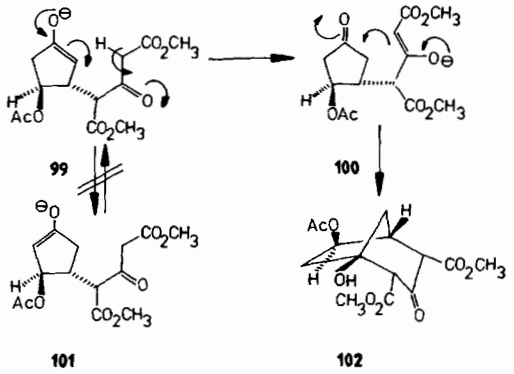
Esters **87a** and **87b** add smoothly and in good yields to **16a**; indeed, an excess of Michael acceptor must be avoided, since otherwise **88a** reacts further to give **90**, which is converted into the thermodynamically more stable unsaturated ketone **92** on treatment with acid. Cleavage of the double bond of this stable product can yield valuable intermediates. Decarboxylation of the homologous compound **88b** affords easy access to the tricyclic lactam **91** *via* a Dieckmann cyclization. Attack at the lactam carbonyl group leads to ring opening with formation of a *cis*-disubstituted cyclopentanone. The potential of this strategy was first studied on ketones of the type **93**, which are readily accessible with acetonedicarboxylic esters[57].

In order to direct the nucleophilic attack of the base at the carbonyl group flanking the ester the *tert*-butyl ester was chosen, and, in order to avoid retro-Michael reactions, the other carbonyl group was ketalized. After ring opening, in the case of the simple compound **96** hydrolyzation and decarboxylation afforded the *cis*-dicarboxylic acid **95**, whose constitution and configuration were established by comparison with authentic material. Various mono- and di-alkylated compounds can be prepared from **93a** and



93b, for example **97** and **98**, which on β-dicarbonyl cleavage yield branched analogues of **96**, from which symmetrical and/or unsymmetrical *cis*-disubstituted cyclopentanones of type **95** can be obtained. In all the additions mentioned so far, the chirality center formed in the first nucleophilic attack excellently directs the second addition; the question now remains whether the chiral center in 4-oxo-2-cyclopentenyl acetate **16a** effects steric direction even in the primary step. This point is of some importance regarding the use of optically-active **16a** as a starting material and the extent of the chirality transfer to be expected. This question can be investigated by suitable manipulation of the acetonedicarboxylate addition.

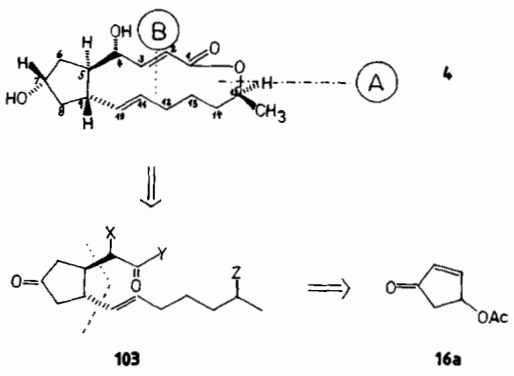




In the formation of products **93a** and **93b** with NaH in tetrahydrofuran (THF), this Michael donor reacts as postulated in Scheme 1. If the reaction is carried out in glyme with potassium *tert*-butoxide as the proton acceptor then proton transfer from the side chain competes with transprotonation in the five-membered ring, which would lead to elimination. The enolate **100** is formed, the ring carbonyl group is regenerated, there is no elimination, and nucleophilic attack at this carbonyl group leads to the bicyclo[3.2.1]octanone derivative **102**. The NMR data obtained for this compound confirm the given configuration, in which the acetoxy group is oriented *trans* to the newly generated C—C bond. There is high steric control, so the chances for chiral transfer seem good. This problem is currently under investigation.

8. Additions—The Route to Brefeldin A

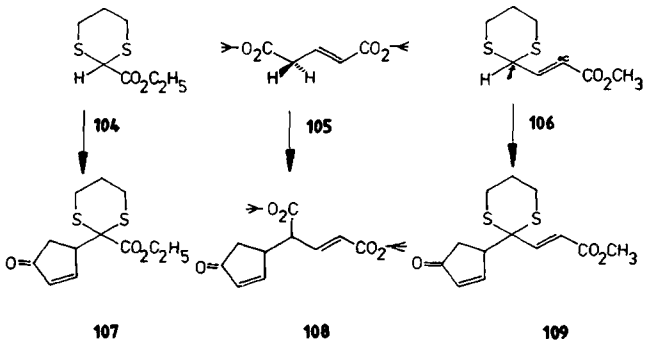
Up to now the Michael donors used have almost exclusively been 1,3-dicarbonyl compounds, and it remains to be seen whether other Michael donors can be successfully employed. The best test of the utility of a synthetic method is its employment in the stereoselective total synthesis of a complex natural product. To test the effectiveness of our preliminary steps and the flexibility of the additions on a specific and important molecule with complicated structure we have chosen the antifungal and cytostatically ac-



tive antibiotic brefeldin A **4**[5]. Its synthesis has already been accomplished by several research groups.

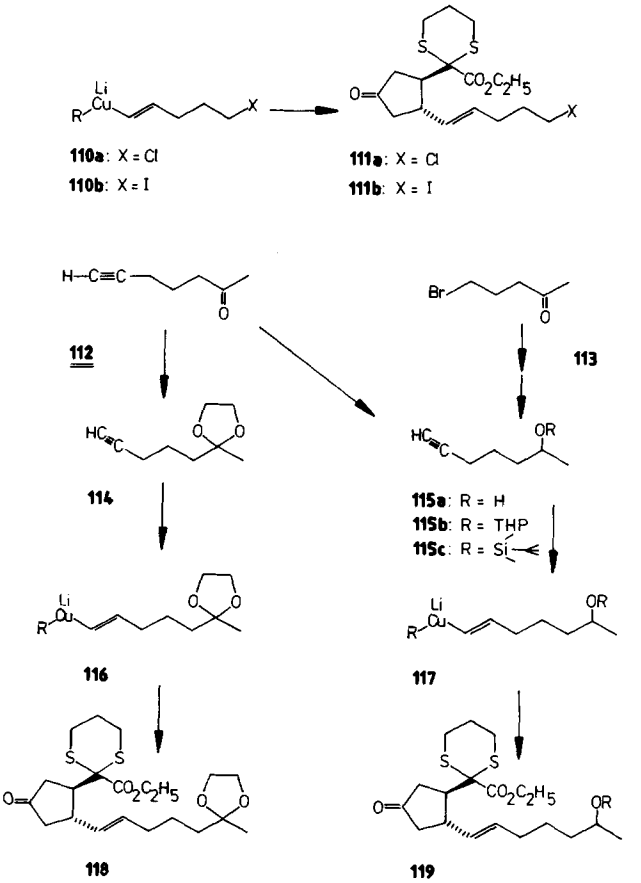
If the lactonization (line A) or the Wittig-Horner cyclization (line B) is envisaged as the ring closure step, then **103** can be regarded as tailor-made for a retrosynthetic analysis to our cyclopentenone synthon **16a**. The task in the retrosynthetic analysis is to break the target molecule up into strategically convenient parts that can be easily synthesized and brought together stereoselectively using reactions with good precedent already reported in the literature or analogous reactions which have been tested in the laboratory on model systems.

Starting from **16a** the "upper" chain would be incorporated as an α-functionalized acetic acid or possibly (in this case) as a γ-functionalized crotonic acid, while a suitably functionalized vinyl cuprate could be visualized for the "lower" chain, thus allowing the necessary 1,4-addition.



Donors **104**, **105**, and **106** looked like promising precursors for the upper chain[58]. **104** smoothly affords the adduct **107** in good yields. Its synthesis on a large scale is also reproducible. Compound **108** can be obtained in high yield by deprotonizing the di-*tert*-butyl ester **105** of glutaconic acid (avoiding self-condensation) with lithium tetramethylpiperidide, but the selectivity of the second addition to the cyclopentenone is disappointing; the acrylic ester group, competing very efficiently for the nucleophile, created selectivity problems[59]. Similar problems are encountered with **109**, which is, in addition, difficult to prepare because the Michael addition shows poor regioselectivity. Even in the nonpolar solvent toluene at −78 °C the required γ-addition product (70%) is accompanied by 30% of the α-addition product. In THF the α-addition product even preponderates, to such an extent that it can be obtained on a preparative scale under these conditions[60].— Thus, the thioketal **107** is, without doubt, the monoadduct of choice, since it fulfills all the requirements as intermediate for the synthesis of the target molecule.

The use of a Gillman reagent[61] for the "lower" chain was decided upon from the beginning. Such reagents, which can be prepared from the corresponding vinyllithium derivatives by reaction with pentynylcopper, are highly nucleophilic, and very readily undergo 1,4-addition. Although on paper there are a large number of possibilities, in practice only a small number of vinyl cuprates generated in this way are suitable[62]. Compounds **110a** and **110b**, which are easily prepared from 5-chloro-1-pentyne by addition of diisobutylaluminum hydride (DIBAH), iodination followed by iodine/lithium exchange, and reaction with 1-pentynylcopper, give good yields of **111a** and **111b**, respectively, and the selectivity with which the intermediary vinyl iodide reacts with butyllithium without attacking the iodine attached to the sp^3 hybridized center is remarkable—particularly in the case of **110b** (Scheme 6).

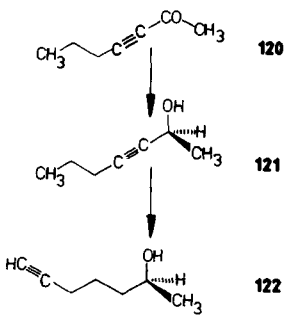


Scheme 6. R = C≡C—CH_2—CH_2—CH_2.

The complete "lower" side chain can be very conveniently incorporated using the acetylene ketone **112**. This can be prepared from methylcyclohexenone by Eschenmoser fragmentation[63]; on reduction it yields the alcohol **115a**, and on ketalization **114**. The alcohol **115a** and its derivatives **115b** and **115c** can also be obtained from the bromoketone **113** by reduction, incorporation of protecting group, and coupling with lithium acetylide.

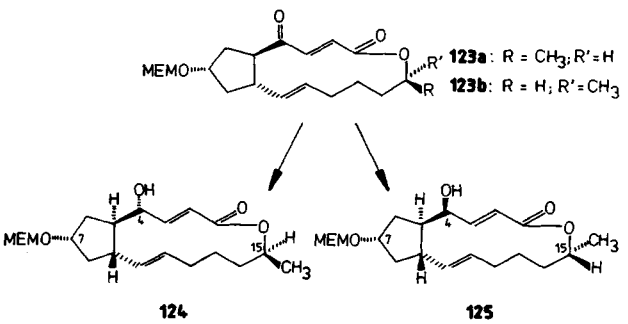
However, in these cases it is not advisable to prepare the vinyl iodide, required for production of the vinyl cuprate, by DIBAH reduction, since side-reactions, such as reductive cleavage of the ketal, occur. Instead tributyltin hydride[64] is used and the resulting intermediate reacted with iodine[65]. The additions of the ketal **116** and of the silyl ether **117c** to **107** are of particular synthetic interest. The tetrahydropyranyl ether **117b**, however, was disappointing; the yield of **119b** is poorer than that of the alcohol **119a** obtained from **117a** *via* the dianion. Although **111a** and **111b** as well as **118** and **119c** are about equally well accessible, the silyl ether **119c** was chosen for further synthesis, since, because of the sp^3 hybridization at the carbon which becomes C 15, all results can be extended di-

rectly to the corresponding chiral silyl ether. Chiral **119c** can also be obtained from ketone **120** by enantioselective reduction with *Mosher*'s reagent[66], whose special merits in the case of acetylene ketones were recognized in a comparative study by *Brinkmeyer* and *Kapoor*[67]. Isomerization of **121** with Kapa[*] using a slightly modified version of the method described by *Brown et al.*[68] drives the triple bond to the end of the chain, thus producing the chiral alcohol **122**, from which the silyl ether can be prepared in the usual way.



119c is an attractive intermediate for the synthesis of brefeldin A; since the configurations at C7 and C15 can be changed it is also useful for the investigation of several selectivity problems peculiar to this ring system.

The observation by *Corey* and *Wollenberg*[69] that the 7-MEM ether[**] of the C15 epimeric ketone **123** can be reduced with excellent stereospecificity, has always proven useful in attempts to synthesize brefeldin A. **123a**, with natural configuration at C15, yields overwhelmingly the alcohol **124**, and thus, finally, brefeldin A, whereas the 4-*epi*-15-*epi* compound **125** can be generated with about the same selectivity from the 15-*epi* compound **123b**.

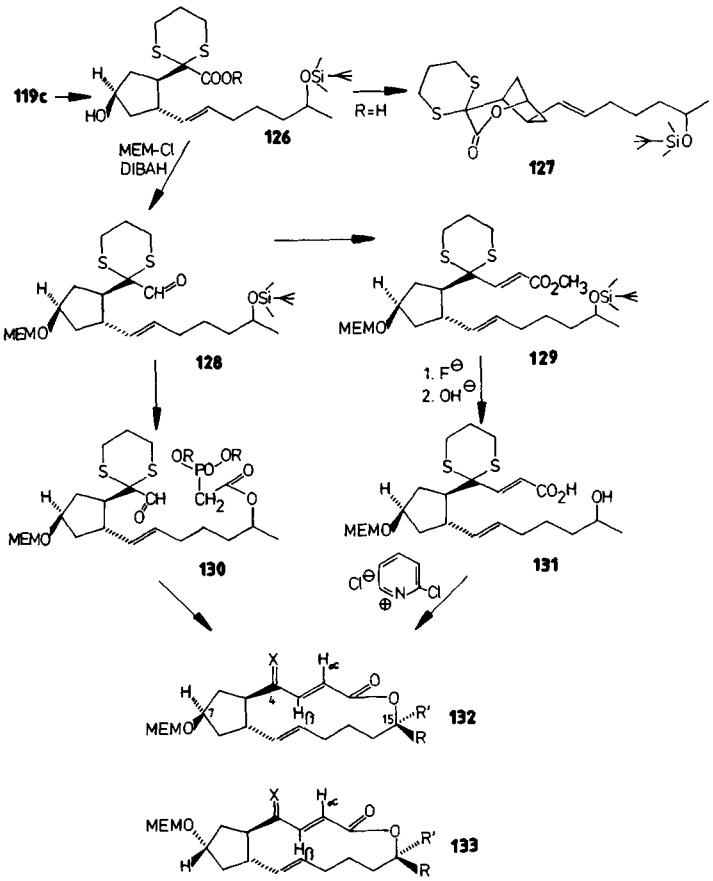


It is unlikely that the distant C15 asymmetric center steers the reduction directly; more plausible is that the configuration at C15 forces the lactone ring to assume a conformation in which the substituents on the ring do not, if possible, enter the ring cavity. *Still*[70] has recently demonstrated typical examples of such conformational stereoselectivity.

The C15 configuration not only affects the reduction but also has a considerable influence on the rate of lactonization[69]. The 4,7-bis-MEM etherated alcohol with natural configuration at C15, cyclizes more rapidly than its epimer. Again different lactone conformations might be responsible. With cyclization, generally product-close transition-states are to be expected, carrying all the strain inherent in the product ring.

To further clarify this point we synthesized both C7 epimeric alcohols and cyclized them using two completely different methods, so that the transition states would be as dissimilar as possible. The influence of C15 on ring conformation ought to be greater than that of C7. We then reduced the C4 ketones in both series, in order to check whether C7 in the close neighborhood really has less effect than the more distant but conformation-dictating C15. This was accomplished in a few stages starting from the easily accessible silyl ether **119c**.

The bulkiness of the dithioketal ensured high stereoselectivity in the production of the β-hydroxy compound **126** by selective reduction of the 7-keto group in **119** with selectride (lithium tri-*sec*-butylhydridoborate). The configuration was confirmed by formation of the lactone **127**[71]. If the carboxy group in **126** is present as MEM ester and the hydroxy group as MEM ether **126** can be reduced directly to the aldehyde **128** using DIBAH in toluene. **128** can be cyclized by both techniques. A Wittig reaction yields the unsaturated ester **129**, which after generation of the free hydroxy acid **131** can be cyclized, using *Mukaiyama*'s[72]



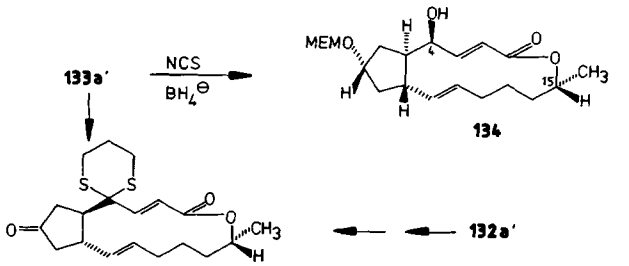
Scheme 7. Substituents of **132** and **133**:

a:	X = S(CH$_2$)$_3$S,	R = CH$_3$,	R' = H
a':	X = S(CH$_2$)$_3$S,	R = H,	R' = CH$_3$
b:	X = O,	R = CH$_3$,	R' = H
b':	X = O,	R = H,	R' = CH$_3$
c:	X = αH,βOH,	R = H,	R' = CH$_3$
d:	X = αOH,βH,	R = CH$_3$,	R' = H

[*] Kapa = Potassium 3-aminopropylamide [68a].

[**] MEM = (2-Methoxyethoxy)methyl; E. J. Corey, J. L. Gras, B. L. Ulrich, *Tetrahedron Lett. 1975*, 617.

pyridinium salt, to the lactone mixture **132a/132a'**. Under these conditions, in the case of the educt **131** the configuration at C 15 has no influence on the lactonization rates: The two C 15-epimeric lactones **132a** and **132a'** are formed in equal proportions (Scheme 7). The situation is quite different for the Wittig-Horner cyclization[73] of phosphonate **130**, which is easily accessible from aldehyde **128** *via* cleavage of the silyl ether and DCCI esterification with phosphonoacetic acid. The cyclization was initiated at room temperature by the slow, controlled addition of a proton acceptor into the solution [$LiOC(CH_3)_3$] or the suspension [NaH], by means of a dosing pump. After 15 hours, almost 50% of the starting material had reacted. The product formed consisted mainly ($\approx 10:1$) of the stereoisomer **132a'**, whose configuration could easily be established[58]. If the configuration at C 7 of the alcohol **126** is inverted, using *Mitsunobus'* reagent[*][74], it can be cyclized like its epimer *via* the aldehyde and phosphonate; here also only one stereoisomer is produced in overwhelming preponderance, namely **133a'** (Scheme 7). This configuration was easily confirmed. Since thioketal cleavage with *N*-chlorosuccinimide (NCS) and reduction with tetrahydroborate leads to **134**, which, after MEM ether-cleavage, yields 4,15-*epi*-brefeldin A, there can be no doubt that the Wittig-Horner cyclization has in this case yielded the 15-*epi*-thioketal **133a'** stereoselectively.



The fact that both cyclization products **133a'** and **132a'** lead to the same ketone **135** after MEM ether-cleavage and oxidation shows that the same stereoselectivity controls the cyclization of the 7β-MEM ether series[58]. The C 15 configuration-dependent conformations in both C 15-epimer series can be seen by comparison of the proton magnetic resonance spectra of **132a** and **133a** with **132a'** and **133a'**. In the series having a "natural" C 15-configuration the signal of the β-proton of the acrylic ester group is observed at $\delta = 7.16$, while in the spectrum of the Wittig-Horner cyclization product having an "unnatural" configuration this is shifted to $\delta = 6.72$. Such a large difference is difficult to explain in terms of the spatial differences caused by a proton or methyl group, and a configuration-dependent conformation with different relative positions and a different degree of immersion into the π system of the double bond between C 10 and C 11 is a much more satisfactory explanation. This suggestion is supported by the fact that such an interaction with the π system can be recognized in the C4,C15-epimeric alcohols **133c** and **133d** on account of the very different signals of H 10 and H 11. In the case of the natural C 15-configuration **133d** the signals of these protons are noticably split, whereas the protons in **133c** exhibit a normal two proton multiplet. Here again a transannular conformational effect is perceptible. To summarize, it emerges that the configuration at C 15 has no effect on the lactonization rate if a dithioketal is present on C 4. *Bartlett et al.*[75] have reported a similar finding for the C 4 ketone. The Wittig-Horner cyclization, on the other hand, unambiguously favors the 15-*epi*-configuration (**132a'**, **133a'**), independent of the configuration at C 7. Hence, one now has a stereoselective cyclization process for both configurations at C 15[76].

Finally, the 4-keto group is reduced. In the case of the C 15-epimeric ketones (**133b** and **133b'**) this leads to brefeldin A and 4,15-*epi*-brefeldin A, respectively[77]. Additionally, the 7β-MEM ethers of type **132** too yield exclusively two alcohols (**132c** and **132d**), the stereoselectivity of the reaction again being determined by the configuration at C 15. Everything points to a conformational effect. It is hardly possible to explain in any other way the fact that the comparatively distant C 15 has a greater influence on the reduction of the ketone group at C 4 directly adjacent to the five-membered ring than the spacial configuration of an MEM-ether group in its close neighborhood.

9. Outlook

The results referred to here, even though they are restricted to a narrow field, give some impression of the many possibilities offered by 4-oxo-2-cyclopentenyl acetate **16a** for the stereoselective and enantioselective synthesis of cyclopentanoid compounds and natural products. The broad field of heteroatom-activated donors and double donors, which lead stereoselectively to various nonaromatic heterocyclic ring systems, has hardly been explored. Such double additions can either lead directly to polycyclic systems or, the heteroatom, *e.g.* sulfur, can serve for further functionalization and/or as a built-in cleavage point. In the case of the monoadducts the main emphasis is on the manifold possibilities of intermolecular and intramolecular cycloadditions guaranteeing regioselectivity. Products such as **72**, **107**, **108** and **109**, open up interesting synthetic pathways, and in this connection it is worth remembering the smooth isomerization to more highly substituted cyclopentenones (see **40**→**41**) in order to correctly assess the flexibility of the methodology. If the correctly substituted product is not available directly as a cyclization product then functionality transformations as they are being intensively studied at the moment can be brought into play. In view of this considerable potential it would appear that 4-oxo-2-cyclopentenyl acetate is a very promising and versatile synthetic building block.

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[*] *Mitsunobus'* reagent = triphenylphosphane/dimethylazodicarboxylate.

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Chain and Ring Phosphorus Compounds—Analogies between Phosphorus and Carbon Chemistry**

By Marianne Baudler*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

Up to about 15 years ago compounds with a skeleton of phosphorus chains or rings were regarded as "exotic" in the field of nonmetal chemistry. Aside from a number of examples of molecules with two P atoms directly bonded to each other and a few sporadically discovered monocyclic ring compounds, only solids of undefined composition and structure were known. Since then the state of our knowledge in this sector has made considerable progress: between PH_3 and its derivatives on the one hand, and the high-molecular modifications of elementary phosphorus on the other, an unexpected variety of well defined compounds have been discovered, showing many similarities to the analogous compounds of carbon. However, surprises can still occur even with "small" phosphorus-containing molecules, as shown by the likewise recently discovered field of phosphorus three-membered ring compounds.

1. Introduction

Compounds with a skeleton of trivalent phosphorus atoms are generally very reactive: they can easily be attacked by oxidation on the free electron pair of the P atoms, and disproportionate like other nonmetal compounds containing homonuclear element-element bonds. Thus, until recent times only a limited number of such compounds were known[1], except for the much earlier investigated tetraorganodiphosphanes $R_2P—PR_2$. In the last decade advances in preparative techniques[2] and in the ability of spectroscopic methods to characterize reactive species led to a considerable broadening of our knowledge of chain and ring-type phosphorus compounds, and concomitantly some striking analogies to carbon chemistry have come to light:

The existence of constitutional and configurational isomers;
valence tautomerism in phosphorus compounds;
stable phosphorus three-membered ring compounds;
the existence of phosphorus compounds with annelated ring systems.

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In this review article we shall demonstrate the similarities between phosphorus and carbon chemistry, discussing the various classes of compounds with P_n skeletons from several points of view.

2. Phosphorus Hydrides (Phosphanes)

All compounds having a skeleton of trivalent phosphorus atoms can be regarded as derivatives of the corresponding phosphorus hydrides (phosphanes). Since 1965 an unexpectedly wide variety of binary phosphorus-hydrogen compounds have been found, in addition to the already long-known hydrides PH_3 and P_2H_4, in the volatile hydrolysis products of calcium phosphide or in the thermolyzates of diphosphane[3a-d]. The present situation is shown in Table 1.

The general formula of the individual phosphanes can be deduced with certainty from their mass spectra. To exclude disproportionation as far as possible during the investigation, the specimens of the substances are introduced directly into the ion source of the mass spectrometer at various vaporization temperatures (−196 °C to +50 °C) by means of a special injection system[7,8]. The ionization takes place by bombardment with 10—12 eV electrons or by field ionization. The identification of the low-hydrogen phosphanes relies on the dependence of the field ionization spectra on the vaporization temperature of the specimens and the different proportions of the individual compounds present in different fractions. The correlation is fully confirmed by means of electron bombardment excitation, by the constant intensity ratios of the corresponding peaks with respect to those of other molecule-ions when

Table 1. Phosphorus hydrides (phosphanes) with more than two P-atoms in the molecule

Phosphanes	P_nH_{n+2}	P_nH_n	P_nH_{n-2}	P_nH_{n-4}	P_nH_{n-6}	P_nH_{n-8}	P_nH_{n-10}	P_nH_{n-12}	P_nH_{n-14}
Triphosphanes	P_3H_5	P_3H_3							
Tetraphosphanes	P_4H_6	P_4H_4	P_4H_2						
Pentaphosphanes	P_5H_7	P_5H_5	P_5H_3	P_5H					
Hexaphosphanes	P_6H_8	P_6H_6	P_6H_4	P_6H_2					
Heptaphosphanes	P_7H_9	P_7H_7	P_7H_5	P_7H_3	P_7H				
Octaphosphanes	P_8H_{10}	P_8H_8	P_8H_6	P_8H_4	P_8H_2				
Nonaphosphanes	P_9H_{11}	P_9H_9	P_9H_7	P_9H_5	P_9H_3				
Decaphosphanes		$P_{10}H_{10}$	$P_{10}H_8$	$P_{10}H_6$	$P_{10}H_4$	$P_{10}H_2$			
Undecaphosphanes			$P_{11}H_9$	$P_{11}H_7$	$P_{11}H_5$	$P_{11}H_3$			
Dodecaphosphanes			$P_{12}H_{10}$		$P_{12}H_6$	$P_{12}H_4$	$P_{12}H_2$		
Tridecaphosphanes						$P_{13}H_5$			
Tetradecaphosphanes						$P_{14}H_6$	$P_{14}H_4$	$P_{14}H_2$	
Pentadecaphosphanes							$P_{15}H_5$		
Hexadecaphosphanes							$P_{16}H_6$	$P_{16}H_4$	$P_{16}H_2$
Heptadecaphosphanes								$P_{17}H_5$	
Octadecaphosphanes								$P_{18}H_6$	$P_{18}H_4$

By analogy with the boranes, the individual compounds are characterized by the number of phosphorus and hydrogen atoms, for example P_3H_5 is triphosphane(5), P_3H_3 is triphosphane(3), *etc.*

The phosphanes make up a number of homologous series with general formulas P_nH_{n+2}, P_nH_n, P_nH_{n-2}, ... up to P_nH_{n-14}. The first series comprises the open-chain phosphanes, the second series the monocyclic compounds (and with more than five P atoms, probably also single rings with side chains), while the other series comprise the low-hydrogen hydrides with condensed ring systems. As can be seen from the synopsis in Table 1, as the phosphorus content of the compound increases, the tendency to form chain-type phosphanes P_nH_{n+2} as opposed to ring compounds shows a marked decrease. From $n=5$ upwards first the monocyclic phosphanes P_nH_n, and from $n=7$ upwards the polycyclic hydrides P_nH_{n-2m} ($m=1-7$) are clearly preferred.

Up to now it has been possible to prepare triphosphane(5)[4], pentaphosphane(5)[5], and heptaphosphane(3)[6] in pure form. The other hydrides have only been isolated and studied in the form of sometimes strongly enriched mixtures. The reason for this is that the very similar properties of the individual compounds, and particularly their marked tendency to disproportionate, makes them very difficult to separate.

the ionization voltage is reduced from 70 eV to the appearance potential. The occasional complete absence of low-phosphorus disproportionation products such as PH_3, P_2H_4, P_3H_3, and P_3H_5 shows that the phosphorus-rich compounds are not formed thermally or by electron bombardment within the mass spectrometer itself. If the measurement conditions mentioned are observed, then clearly the results will hardly be influenced by any simultaneous disproportionation of the phosphanes in the mass spectrometer. In contrast, if the specimen temperature is increased to above 100 °C, or if the ionization voltage is raised above 15 eV, rearrangement or decomposition reactions clearly become predominant.

In addition to this, triphosphane(5), tetraphosphane(6), pentaphosphane(7), and pentaphosphane(5) have been characterized by a complete analysis of their phosphorus nuclear magnetic resonance spectra (see Sections 2.1 to 2.4). Compared to mass spectroscopy, this method has the advantage that the phosphane specimens can be investigated below room temperature and possibly in solution, so that disproportionation reactions can be reliably excluded. However, in the case of compounds with high phosphorus and low hydrogen contents, the applicability of nuclear magnetic resonance spectroscopy for characterization purposes is often limited by unduly low solubilities[9]. Satisfactory agreement is generally obtained between the composi-

tions determined for phosphane mixtures by mass spectrometry and by NMR spectroscopy.

The higher phosphanes with more than two phosphorus atoms in the molecule are generally relatively volatile. Their spontaneous combustibility in air gradually decreases with increasing phosphorus content. In contradiction to many statements in the literature and in textbooks, diphosphane and its higher homologs are not explosive: they burn quietly in atmospheric oxygen, giving a white smoke of phosphorus pentoxide. However, explosions with phosphanes can arise in two ways: the product mixture contains hydrogen at the same time, as is possible in the volatile hydrolysis products of metal phosphides; then, in presence of oxygen an explosive gas mixture is produced, which is ignited by the spontaneously flammable phosphane. Also, when phosphanes disproportionate one of the end products is PH_3, whose boiling point lies at $-88\,^{\circ}C$; thus, sealed glass ampoules containing phosphane specimens can suddenly be destroyed by explosion, even when cooled in dry ice, owing to the build-up of PH_3 pressure. On the other hand, the disproportionation, which takes place to an appreciable extent already above $-30\,^{\circ}C$, and which is greatly accelerated by heat and light, gives rise to phosphorus-rich, solid, yellow decomposition products. The phosphanes of the series P_nH_{n+2} and P_nH_n from $n=3$ upwards can be dissolved in diphosphane, molten white phosphorus, cyclooctatetraene, and the hydrocarbon mixtures 1-methylnaphthalene/phenanthrene and toluene/phenanthrene[7,8]. While the phosphorus-rich hydrides are clearly stabilized in the white phosphorus and the aromatic solvents, the solutions in diphosphane are extremely unstable and tend to decompose spontaneously. A violent reaction sometimes takes place with chlorinated hydrocarbons.

2.1. Triphosphane(5)

The first indication of the existence of triphosphane(5) **1** was given by the presence of an excessive number of lines in the Raman spectrum of diphosphane, P_2H_4[10]. The increase in the intensity of these attendant lines when the specimen was illuminated or warmed, with simultaneous evolution of PH_3, led to the conclusion that the diphosphane was undergoing disproportionation with **1** as the product:

$$2\,P_2H_4 \rightarrow \underset{\mathbf{1}}{P_3H_5} + PH_3$$

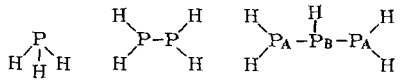
Mass-spectrometric identification of the compound was achieved by *Royen et al.* in 1964, who decomposed small amounts of Mg_3P_2 and Ca_3P_2 mixed with the corresponding arsenides, nitrides, or germanides with dilute hydrochloric acid, directly at the mass spectrometer[11]. Shortly afterward fractions strongly enriched in **1** could be isolated on a preparative scale during the separation of the reaction products of commercial calcium phosphide[12] with pure water[3a,b]. At approximately the same time, *Fehlner*[13] detected the formation of **1** mass spectrometrically in the thermolytic and photolytic decomposition of diphosphane.

In 1968 *Fehlner* described a process for the gas-phase photolysis of diphosphane in a closed-circuit apparatus, by means of which about 10 mg of 95%-pure **1** was obtained in 100 min[14,15]. The chain structure of **1** was established in 1972, by analysis of the $^{31}P\{^1H\}$-NMR spectrum[16].

In recent years we were able to develop a reproducible process for the production of nearly pure **1** in milliliter quantities by the thermolysis of liquid diphosphane at normal pressure followed by fractionation of the thermolyzate[4]. In a typical experiment 81 mL[17] of highest-purity P_2H_4 was subjected to thermolysis for 25 h at 35 °C, yielding in the first instance 63 mL of clear yellow thermolyzate with a content of **1** amounting to about 20% of the total phosphorus in the reaction mixture (P-%). At this stage the thermolysis was stopped to avoid any further reaction of **1** and formation of solid phosphorus hydrides, which initiate autocatalytic decomposition of the thermolyzate. Compound **1** was then isolated by cocurrent distillation in a mixture with P_2H_4 (pressure 10^{-4} torr, bath temperature -40 to $+90\,^{\circ}C$) followed by fractional condensation. At $-40\,^{\circ}C$ 9.1 ml of a condensate of highly enriched **1** (86.9 P-%) was obtained, which still contained some P_2H_4 and P_4H_6, and at $-196\,^{\circ}C$ 45 mL of P_2H_4. By repeated distillation, the purity of **1** was improved to 96%. The degree of difficulty of the process is comparable to that of the preparation of diphosphane[18].

1 is a colorless liquid which in the absence of air and light remains stable for many days at $-80\,^{\circ}C$. At room temperature and in diffuse daylight it rapidly turns yellow and later decomposes to give yellow solid products.

The triphosphane **1** can be regarded as a derivative of monophosphane **2** and diphosphane **3**, in which individual hydrogen atoms have been replaced by the bulkier PH_2 group. This substitution increases the bond angle at the



2 **3** **1**

phosphorus, as shown by the parameters of the ^{31}P-NMR spectrum[4] (see Table 2): the δ-downfield shift in the sequence **2**—**3**—**1** and the increase in the absolute value of the negative $^1J(PP)$ coupling constant following the transformation of **3** into **1** are, according to current experience[20], attributable to a change in the hybridization of the phosphorus—increasing s-character of the bonding orbitals. The relative high-field position of the P_B signal of **1** provides evidence that the hydrogen in the PH group is more acidic.

Table 2. ^{31}P-NMR parameters of P_3H_5 (**1**), P_2H_4 (**3**), and PH_3 (**2**), solvent-free, **1** and **3** at 213 K, **2** at 183 K [a].

Phosphane	δ	$^1J(PP)$	Ref.
1	P_A: −156.7 P_B: −173.2	−146.6	[4]
3	−205.0	−108.2 [b]	[16]
2	−235.1		[16]

[a] δ-Values with *negative* sign for *upfield* shift; coupling constants in Hz. [b] Determined from the ^1H-undecoupled room-temperature spectrum [19].

Table 3. Raman spectrum of P_3H_5 (**1**), solvent-free, 193 K. Frequencies, relative intensities (0 to 100) with polarization filter (parallel to the E-vector of the laser light), degree of depolarization $\rho_{p\perp}$, state of polarization, and assignment of the bands.

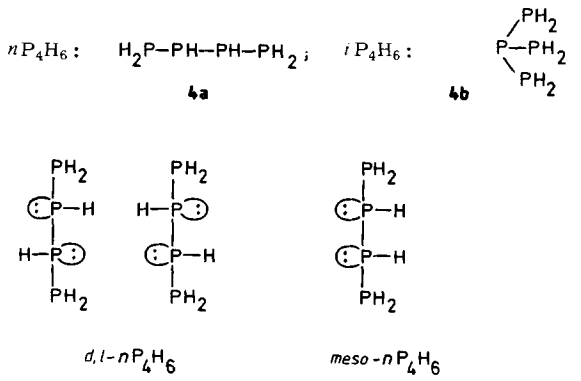
Frequency [cm^{-1}]	Int.	Degree of depolarization State of polarization	Assignment
158	15	0.42 (p)	δ(PPP)
414	63	0.08 (p)	ν_s(PP)
457	14	0.68 (dp)	ν_{as}(PP)
610	1	0.00 (p)	δ(HPP)
655	1	0.00 (p)	δ(HPP)
717	4	0.11 (p)	δ(HPP)
747	1	0.00 (p)	δ(HPP)
835	2	0.00 (p)	δ(HPP)
883	2	0.34 (p)	δ(HPP)
1062	5	0.44 (p)	δ(HPH)
2267	100	0.19 (p)	ν(PH)

The broadening of the angle at the central phosphorus atom has been confirmed from the Raman spectrum of **1**[4] (see Table 3). If the molecule is treated to a first approximation as a three-mass model of the C_{2v} point group[21], the PPP valence angle is obtained as 104.5° ($\sphericalangle$HPH in **2**: 93.8°[22]; $\sphericalangle$HPP in **3**: 95.2°[23]). The valence force constant of the P—P bond amounts to 1.77 mdyn/Å and the deformation constant of the PPP valence angle to 0.15 mdyn/Å.

2.2. Tetraphosphane(6)

Heating of liquid diphosphane and triphosphane(5) gives rise to phosphane mixtures containing varying amounts of tetraphosphane(6) **4**[3,7,8]. Initially, the diphosphane and triphosphane thermolyzates consist only of chain-type hydrides, which, when the thermolysis is continued, react further in part to form pentaphosphane(5) **5**. Clearly, the formation of the cyclopentaphosphane is thermodynamically more favorable, and is in any case accelerated by autocatalysis. Phosphane mixtures with a content of **4** of 35—40 P-% in addition to **1** (about 55 P-%), **3** (5—10 P-%), and **5** (<5 P-%) are obtained from diphosphane thermolyzates (see Section 2.1) by removal of **2** and **3** at −40 °C under high vacuum[8]. In this way 100 mL of **3** can be made to yield about 15 mL of a markedly tetraphosphane-rich, solid-free, yellow phosphane mixture of medium viscosity. Further enrichment of **4** by distilling off **1** is impossible, because this causes further disproportionation, with the formation of **5**. The highest content of **4**, amounting to 48 P-%, has been obtained by the thermolysis of pure **1** at +10 °C under high vacuum[7].

Beginning with tetraphosphane(6), the structural problem of the chain-type phosphanes becomes increasingly complex as a result of isomerism. If an unbranched phosphorus chain is present, **4** should be characterized in the $^{31}P\{^1H\}$-NMR spectrum by an AA'BB' system for the two different types of P atoms (in the middle and at the ends of the chain). However, the spectrum obtained in practice contains considerably more lines (Fig. 1). According to the complete analysis of the spectrum[24], there are two reasons for this: in the first place, when either **3** or **1** is subjected to thermolysis, **4** is always formed as a mixture of the two constitutional isomers, with unbranched and branched



phosphorus chains (**4a** and **4b**). To the branched isomer **4b**, which can be regarded as tris(phosphino)phosphane, there corresponds an A_3B spin system (Fig. 1e).

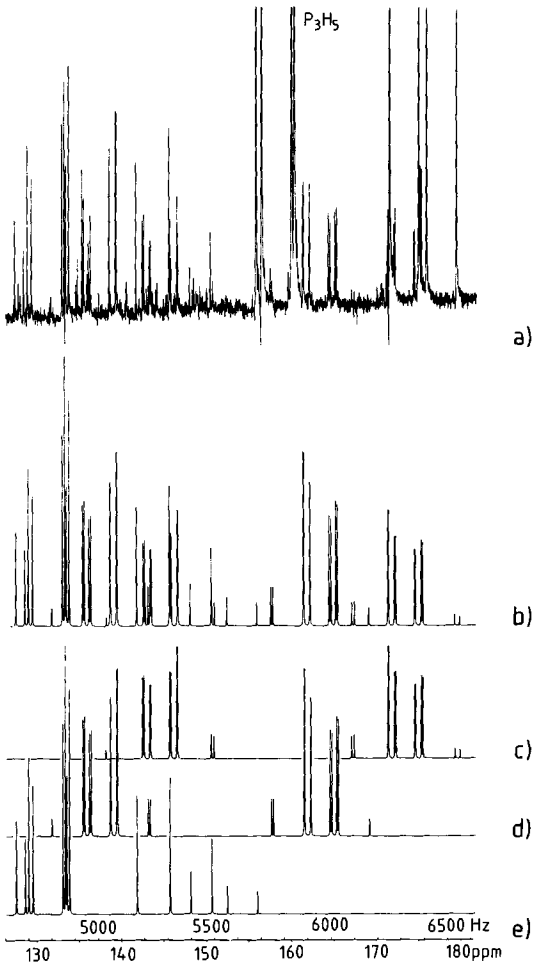


Fig. 1. $^{31}P\{^1H\}$-NMR spectrum of a P_3H_5/P_4H_6 mixture at 190 K (36.434 MHz). a) Observed spectrum; the eight intense signals correspond to the A_2B system of P_3H_5. b) Calculated spectrum of P_4H_6. c)—e) Separate simulation of the individual isomers (*d,l-n*P_4H_6, *meso-n*P_4H_6, *i*P_4H_6).

On the other hand, in isomer **4a** both of the middle P atoms are chiral centers, since each of them has three different substituents and a free electron pair. Assuming that the inversion at the P atoms is slow in comparison with the NMR timescale, which is plausible in the case of chain-type phosphanes below room temperature[25], there will

then be two configurational isomers that can be distinguished by NMR spectroscopy, namely the *d,l*- and the *meso*-forms. Both diastereomers are characterized by an AA'BB' system (Fig. 1c and d, respectively), that of the *meso*-isomer being shifted somewhat downfield[26]. Superimposition of the calculated individual spectra (Fig. 1b) reproduces the experimental P_4H_6 spectrum very satisfactorily. At the same time, this provides a clear indication of the existence of isotetraphosphane(6) and of the two configurational isomers of *n*-tetraphosphane(6). The relevant ^{31}P-NMR parameters and the relative isomer frequency are summarized in Table 4[24].

Table 4. ^{31}P-NMR parameters of iP_4H_6 (**4b**), *meso*-nP_4H_6 (*meso*-**4a**), and *d,l*-nP_4H_6 (*d,l*-**4a**) in a P_3H_5/P_4H_6 mixture at 190 K; *J* in Hz.

$(H_2P_A)_3P_B$	$H_2P_B—P_AH—P_{A'}H—P_{B'}H_2$	
4b	*meso*-**4a**	*d,l*-**4a**
30.2%	41.7%	28.1%
$\delta_A = -131.3$	$\delta_A = \delta_{A'} = -137.5$	$\delta_A = \delta_{A'} = -144.6$
$\delta_B = -147.6$	$\delta_B = \delta_{B'} = -163.0$	$\delta_B = \delta_{B'} = -173.0$
$J_{AB} = -178.7$	$J_{AB} = J_{A'B'} = -163.8$	$J_{AB} = J_{A'B'} = -168.2$
	$J_{AA'} = -168.5$	$J_{AA'} = -181.2$
	$J_{A'B} = J_{AB'} = +24.2$	$J_{A'B} = J_{AB'} = +25.7$
	$J_{BB'} = -3.0$	$J_{BB'} = +7.1$

The ratio of **4a** to **4b** is influenced by the method of production of (**4**): in the thermolyzates of **1** the fraction of **4b** is always smaller than that in the thermolyzates of **3**. Very probably **4a** is formed preferentially according to reaction (a), and **4b** according to reaction (b).

$$\underset{\mathbf{1}}{P_3H_5} + \underset{\mathbf{1}}{P_3H_5} \rightarrow \underset{\mathbf{4a}}{H_2P—PH—PH—PH_2} + \underset{\mathbf{3}}{P_2H_4} \quad (a)$$

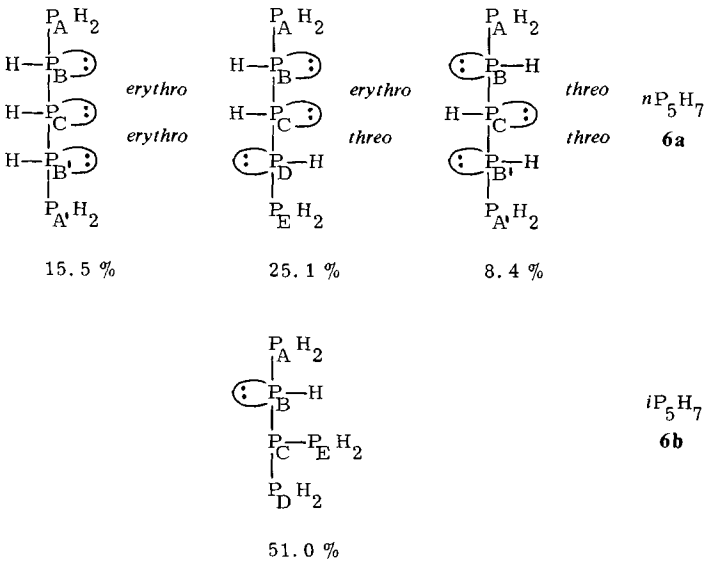
$$\underset{\mathbf{3}}{P_2H_4} + \underset{\mathbf{1}}{P_3H_5} \rightarrow H_2P—\underset{\displaystyle PH_2}{\underset{|}{P}}—PH_2 + \underset{\mathbf{2}}{PH_3} \quad (b)$$

4b

2.3. Pentaphosphane(7)

Phosphane mixtures of P_2H_4 thermolyzates or fractions of the diphosphane preparation with a high content of **1** and **4** show, in their $^{31}P\{^1H\}$-NMR spectra, additional low-intensity signal groups between -100 and -180 ppm, which correspond to pentaphosphane(7), **6**[27]. The proportion of **6** is at the most 5—10 P-%. Any further enrichment leads to decomposition with the formation of cyclophosphanes. **6** is not stable for long periods even at $-70\,^\circ C$. Clear proof of the existence of **6** and of its structural arrangement is based on a complete analysis of the $^{31}P\{^1H\}$-NMR spectrum[27,28]. According to the latter, all four of the possible isomers distinguishable by NMR spectroscopy, namely *d,l*-isopentaphosphane(7) **6b** and the three diastereomers of *n*-pentaphosphane(7) **6a** (*erythro/erythro*, *erythro/threo*, and *threo/threo*) coexist; of these, **6b** shows the highest relative frequency.

Together with the data concerning the low-phosphorus homologs, the ^{31}P-NMR parameters of **6** make it possible to derive general relationships for the chemical shifts and the ^1J(PP)-coupling constants of chain-type phosphanes as



a function of their structural parameters (*a, b, c:* number of phosphorus atoms in the α, β, and γ positions)[29]:

$$\delta(^{31}P) = -224.7 + 26.4a + 33.7b - 6.0c$$
$$^1J(PP) = -110.5 - 31.6a - 13.0b + 1.9c$$

Clearly, the chemical shifts depend strongly on the chain length and the extent of the branching: α and β PH_2 groups bring about a strong downfield shift, the β-effect being still greater than the α effect. γ PH_2 groups bring about a slight upfield shift. It should be noted that in alkanes, though the displacement increments for α, β, and γ carbons[30] are quantitatively smaller, they are of the same sign as, and of similar magnitude ratios to the corresponding increments in the case of the chain-type phosphanes. These relationships allow predictions concerning the appearance of the ^{31}P-NMR spectra of the various structurally isomeric phosphanes P_nH_{n+2} with $n = 6$—9. This offers the prospect of being able to characterize these extremely unstable homologs, obtainable only in low concentrations, not only by mass-spectrometry but also by ^{31}P-NMR spectroscopy.

2.4. Pentaphosphane(5)

When phosphane mixtures with a high content of **1** and **4** are subjected to mild thermolysis ($-20\,^\circ C$, high vacuum), the main product formed is cyclopentaphosphane **5**[5].

$$\underset{\mathbf{1}}{P_3H_5} + \underset{\mathbf{4}}{P_4H_6} \rightarrow \underset{\mathbf{5}}{P_5H_5} + 2\,\underset{\mathbf{2}}{PH_3}$$

$$\underset{\mathbf{4}}{P_4H_6} + \underset{\mathbf{4}}{P_4H_6} \rightarrow \underset{\mathbf{5}}{P_5H_5} + \underset{\mathbf{3}}{P_2H_4} + \underset{\mathbf{2}}{PH_3}$$

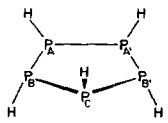
Since **2** and **3** are removed continuously from the reaction system, the final residue of a low-temperature vacuum thermolysis of this type consists of highly enriched **5** (about 80 P-%), in addition to **2**, **3**, **1**, **4**, and other phosphorus hydrides, which give ^{31}P-NMR signals between $\delta = +50$ and -80 and very probably also have cyclic

structures. Largely pure **5** (96 P-%) can then be obtained as a dilute and relatively stable solution by extraction with aromatic hydrocarbons and subsequent removal of the more volatile hydrides under vacuum[5]. The methanolysis of tetrakis(trimethylsilyl)cyclotetraphosphane **7** also leads to **5** *via* a complex reaction, the product being obtainable in 97% purity[31,32].

$$\underset{\mathbf{7}}{(Me_3SiP)_4} \xrightarrow[-Me_3SiOMe]{+MeOH} \underset{\mathbf{5}}{P_5H_5}$$

The compound is positively identified from the mass spectrum (20 eV, 23 °C) with a high relative intensity of the M^+ ion ($m/z = 160$; rel. int. 97%), and in particular from the AA'BB'C spin system in the $^{31}P\{^1H\}$-NMR spectrum (Fig. 2, Table 5)[7].

Table 5. ^{31}P-NMR parameters of P_5H_5 (**5**) in 1-methylnaphthalene/phenanthrene (≈ 1%) at 300 K; J in Hz.



$\delta_A = \delta_{A'}$	=	− 36.4
$\delta_B = \delta_{B'}$	=	− 31.7
δ_C	=	− 9.9
$J_{AA'}$	=	−234.6
$J_{AB} = J_{A'B'}$	=	−220.6
$J_{BC} = J_{B'C'}$	=	−219.4
$J_{AB'} = J_{A'B}$	=	+ 27.5
$J_{AC} = J_{A'C}$	=	+ 31.6
$J_{BB'}$	=	+ 44.3

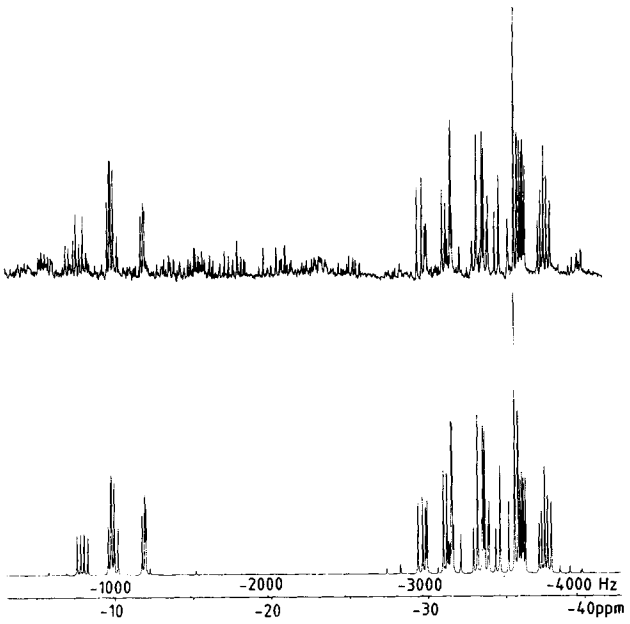


Fig. 2. Observed (upper) and calculated (lower) $^{31}P\{^1H\}$-NMR spectrum of P_5H_5 in 1-methylnaphthalene/phenanthrene (≈ 1%) at 300 K (101.25 MHz).

From the calculated ^{31}P-NMR parameters it is evident that the configurational isomer obtained is the one with the maximum *trans*-arrangement of the adjacent free electron pairs or hydrogen atoms. **5** is the basic compound of the long-known pentaorganocyclopentaphosphanes, $(PR)_5$[1], which according to the results of X-ray structure analysis show the same configuration for $R = CF_3$[33] and C_6H_5[34].

2.5. Heptaphosphane(3)

Heptaphosphane(3) **8** is one of the phosphorus-rich hydrides with a particularly high tendency of being formed. Thus, it can always be detected in considerable concentrations by mass spectrometry in fractions from the preparation of diphosphane and in P_2H_4 thermolyzates[3b]. According to *von Schnering*[35], it is also observed as the main product in the mass spectrum of the hydrolysis products of Ba_3P_{14} and Ba_2P_7Cl. Preparative amounts of pure **8** can be obtained[6] by mild solvolysis of the trimethylsilyl compound **9**[36,6].

$$\underset{\mathbf{9}}{(Me_3Si)_3P_7} \xrightarrow[-3\,Me_3SiOMe]{+3\,MeOH} \underset{\mathbf{8}}{P_7H_3}$$

In this case **8** occurs in the form of white flakes which turn pale yellow on drying and persistently retain traces of the solvent. On contact with atmospheric oxygen there appears to be no change, but subsequent mass spectrometry reveals the presence of P_7H_3O[37]. On prolonged exposure to water a number of phosphorus acids are formed. The X-ray amorphous substance is completely insoluble in aliphatic and aromatic hydrocarbons, alcohols, ethers, acetonitrile, carbon disulfide, dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric acid triamide, as well as in **3** and in molten white phosphorus. This phenomenon is attributable to a still unexplained process of physical aggregation, which is also observed in substituted polycyclic phosphanes P_nR_m ($m < n$) with small organic groups R (see Section 6). The aggregation forces are relatively weak, since **8** occurs with a high intensity in the mass spectrum (12 eV) already at a vaporization temperature of 60 °C, and can be transformed by metalation directly into derivatives with discrete $P_7H_2^-$, P_7H^{2-}, and P_7^{3-} anions (see Section 3). The compound **8** has a remarkable thermal stability; it decomposes and turns red at about 300 °C.

The tricyclic structure of **8** can be reliably ascertained by analogy of the molecular vibration spectra[6] with those of metalated derivatives of known structures (see Section 3).

3. Metalated Phosphanes

Since the structures of metal phosphides have already been reviewed in recent years[35,38], in what follows we shall only deal with the compounds obtained by direct metalation of phosphanes. In common with the entire chemical behavior of the higher PH_3 homologs—except for their self-ignition in air and their easy disproportionation—their metalation has also never been studied until very recently.

3.1. Trilithium Heptaphosphide

3 reacts with *n*-butyllithium or lithium dihydrogen phosphide with simultaneous disproportionation to give trilithium heptaphosphide **10** and phosphane **2**; in the first case *n*-butane is also formed[6].

$$9\,P_2H_4 + 3\,n\text{BuLi} \xrightarrow[-20\,^\circ C]{\text{THF}} \underset{\mathbf{10}}{Li_3P_7} + 11\,PH_3 + 3\,n\text{BuH}$$
$$\mathbf{3} \qquad\qquad\qquad\qquad \mathbf{2}$$

$$9\,P_2H_4 + 3\,LiPH_2 \xrightarrow[-20\,^\circ C]{\text{Monoglyme}} Li_3P_7 + 14\,PH_3$$

The first step is undoubtedly the metalation of **3** to lithium trihydrogen diphosphide **11**, which immediately reacts further with an excess of **3** with disproportionation and transmetalation to give the triphosphide **12**. The latter under-

$$\underset{\mathbf{11}}{LiH_3P_2} + \underset{\mathbf{3}}{P_2H_4} \rightarrow \underset{\mathbf{12}}{LiH_4P_3} + PH_3$$

goes an analogous transformation to that of **11**, so that tetraphosphides, pentaphosphides, *etc.* are produced in succession. Since the PH groups in phosphanes are generally more acidic than PH_2 groups[4,24], and are therefore also preferentially metalated, not only do chain branchings occur preferentially but also polycyclic compounds can be formed in addition to monocyclic ones.

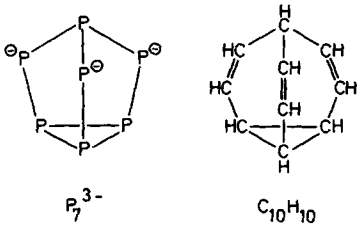
A similar complex reaction results in the nucleophilic cleavage of white phosphorus with lithium dihydrogen phosphide, in which once more **10** is produced as the end product in a yield of 95%[39].

$$3\,P_4 + 6\,LiPH_2 \rightarrow \underset{\mathbf{10}}{2\,Li_3P_7} + 4\,PH_3$$

10 is stabilized by the addition of three solvent molecules (tetrahydrofuran, monoglyme), whose removal leads to decomposition. With chloro(trimethyl)silane the silyl compound **9**, obtained by *Fritz et al.* in another way[36], and with methyl bromide the methyl derivative P_7Me_3 **13**[40], are produced.

The structure of the P_7 skeleton has already been elucidated by *von Schnering* by X-ray structure analysis in the case of the compounds Sr_3P_{14}[41], Ba_3P_{14}[42], and **9**[43]: it is a tricyclic cage, analogous to P_4S_3.

The low-temperature ^{31}P-NMR spectrum of **10**[6] (Fig. 3) shows three separate groups of signals at $\delta = -57$, -103, and -162 in the intensity ratio of 1 : 3 : 3, corresponding to the three different types of phosphorus atoms (at the apex, in the negatively charged bridges, and in the three-membered ring). According to the result of a complete spectrum analysis[44], the finely split "doublet" in the high-field region and the low-field "quartet" correspond respectively to the P atoms in the three-membered ring and to the single atom at the apex, while the pseudo-triplet is produced



P_7^{3-} $C_{10}H_{10}$

by the P-nuclei bound to the lithium. Surprisingly, increasing line-broadening sets in above $-35\,^\circ C$, until at room temperature the only remaining observable feature is a nonspecific broad signal. A further rise of the temperature produces at $+50\,^\circ C$ as the average spectrum a singlet at $\delta = -119$, which becomes completely sharp at $+80\,^\circ C$ (in monoglyme). The low-temperature spectrum reappears on cooling.

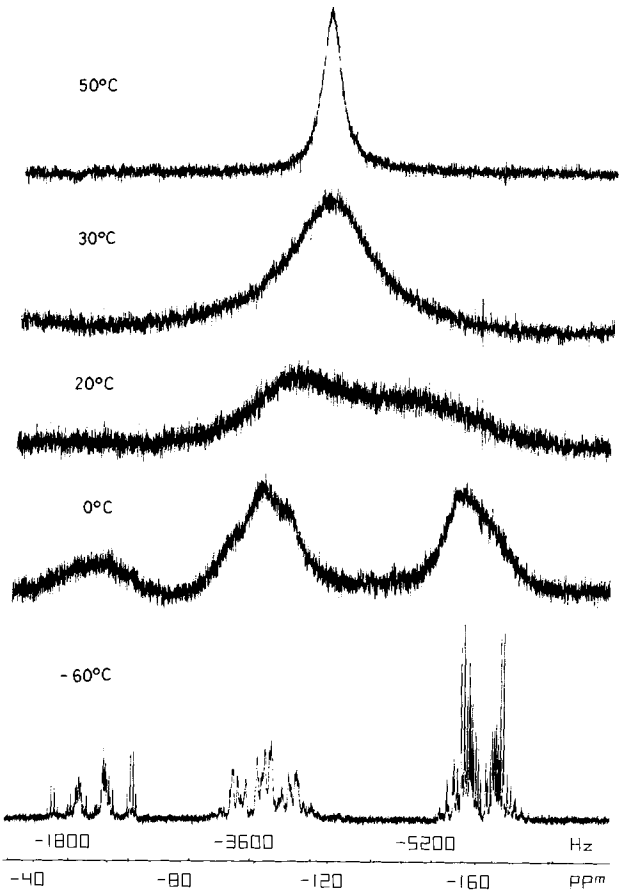
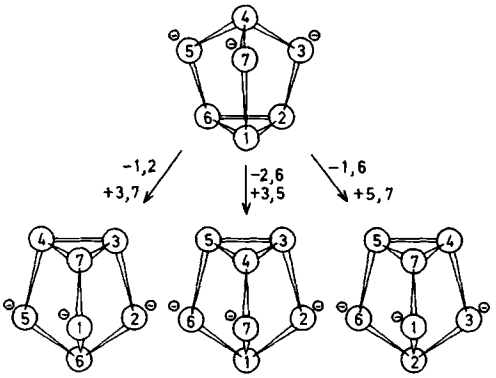


Fig. 3. ^{31}P-NMR spectrum of Li_3P_7 in [D_8]-tetrahydrofuran (saturated at 195 K) as a function of temperature (36.434 MHz).

The reversible temperature variation of the ^{31}P-NMR spectrum of **10** is caused by a dynamic process known as reversible valence tautomerism (degenerate Cope rearrangement)[45] and has been thoroughly investigated in carbon chemistry in the case of bullvalene[46a-c]. In fact, the P_7^{3-} ion and the $C_{10}H_{10}$ hydrocarbon have three essential structural elements in common: they each contain a three-membered ring which markedly reduces the activation energy for the Cope rearrangement, and in addition a threefold symmetry axis and three easily-movable electron pairs.

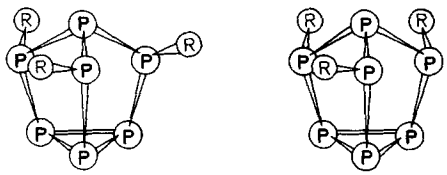
In the course of the intramolecular rearrangement of the P_7^{3-} ion P—P bonds are continually broken and new ones formed, and on account of the threefold symmetry axis, the anion is repeatedly re-formed.

By means of three reversible Cope rearrangements of equal statistical weight, each involving the breaking of one bond in the three-membered ring ($-1,2$ or $-2,6$ or $-1,6$) and the formation of a new P—P bond ($+3,7$ or $+3,5$ or $+5,7$), the P atoms in the three-membered ring are successively transformed into bridge phosphorus atoms, while the original bridge atoms change into three-membered ring



atoms with migration of the electron pairs. Each of the seven phosphorus atoms can end up in any of the possible positions by appropriate further rearrangements, so that in all there are $7!/3 = 1680$ valence-tautomeric forms. At room temperature this dynamic process is rapid in comparison with the NMR time scale, so that all seven P atoms are equivalent. The activation enthalpy ($\Delta H^{\neq} = 59.12$ kJ/mol) calculated by *Gleiter et al.*[47] agrees well with the temperature-dependent ^{31}P-NMR studies, and is of the same order of magnitude as in bullvalene ($\Delta H^{\neq} = 53.53$ kJ/mol)[48]. Accordingly, the P_7^{3-} ion is a typical fluctuating molecule.

The valence tautomerism is naturally limited to the heptaphosphide *ion*. In the methyl compound **13** the substituents are fixed by covalent bonds at the bridge phosphorus atoms. Since the configuration of the latter is not specific in the methylation of **10**, **13** is obtained as a mixture of

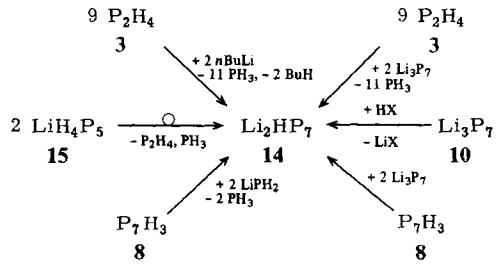


13a **13b**

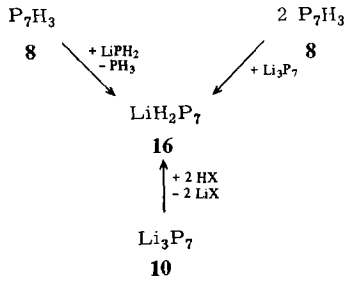
two isomers (**13a** and **13b**), of which, for steric reasons, **13a** is preferred over a statistical frequency distribution[40].

3.2. Dilithium Hydrogen Heptaphosphide and Lithium Dihydrogen Heptaphosphide

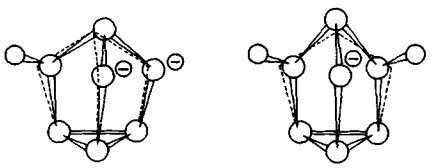
In the metalation of **3** with *n*-butyllithium a red-orange oil appears before the formation of **10**; this consists essentially of dilithium hydrogen heptaphosphide **14**[49]. Pure **14** can be obtained by reacting **3** with Li_3P_7 (4.5 : 1), and is isolated by low-temperature crystallization as a bright orange solvent adduct[49]. **14** is also formed in the partial metalation of P_7H_3 **8** with $LiPH_2$ or **10**, and in the decomposition of lithium tetrahydrogen cyclopentaphosphide **15** and the partial protolysis of **10**[49].



Lithium dihydrogen heptaphosphide **16** is also produced under modified stoichiometric conditions in the lithiation of **8** or the protolysis of **10**[50]. The best way to prepare it is by reacting **8** with Li_3P_7 at $-78\,^{\circ}C$, when it is obtained as a bright orange, amorphous solvent adduct[50].



The composition and the structure of **14** and **16** are established by a complete analysis of their ^{31}P-NMR spectra. In the case of **16** it was only possible to analyze the spin system for the symmetric isomer **16a** (see Table 6)[49,50]. As shown by the NMR parameters, the P_7 cage in **14** and **16**



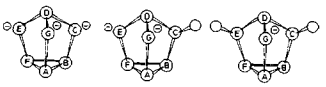
14 **16**

is clearly distorted compared with **10** (shown by the broken lines), as a result of the partial hydrogen substitution.

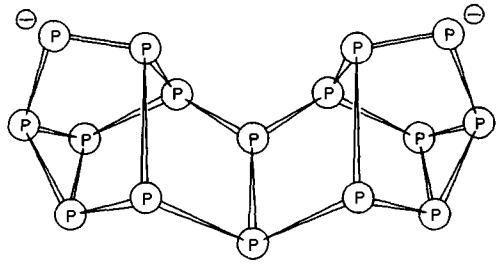
Like dihydrobullvalene, **14** should be capable of a degenerate Cope rearrangement between two valence tautomers. According to temperature-dependent ^{31}P-NMR studies[49] coalescence signals develop as the temperature is raised, thus confirming such a process.

At room temperature **14** and **16** decompose with the formation of dilithium hexadecaphosphide **17**, which can be isolated in the form of large octahedral crystals as a solvent adduct. The P_{16}^{2-} ion shows the constitution recently determined by *von Schnering et al.*[38,51] in the case of the Ph_4P^+ salt by X-ray structure analysis, as is evident from the six signal groups (intensity ratios 2 : 1 : 1 : 1 : 1 : 2) in the ^{31}P-NMR spectrum of **17** (Fig. 4).

Table 6. ^{31}P-NMR parameters of Li_3P_7 (**10**) [44], Li_2HP_7 (**14**) and LiH_2P_7 (symmetrical isomer **16a**), in each case in tetrahydrofuran (saturated), **10** and **14** at 213 K, **16a** at 193 K; J in Hz.



δ_D	− 57.0	− 67.5	− 79.2	$\delta(P_{apex})$
δ_C		− 9.0	0.0	
δ_E	−103.0	−119.4	0.0	$\delta(P_{bridge})$
δ_G		− 83.7	− 45.4	
δ_A		−145.2	−113.1	
δ_B	−161.7	−215.9	−199.8	$\delta(P_{three\text{-}membered\ ring})$
δ_F		−134.8	−199.8	
J_{CD}		−277.6	−226.6	
J_{DE}	−265.3	−304.7	−226.6	$^1J_{PP}$(apex—bridge)
J_{DG}		−316.9	−366.8	
J_{AG}		−398.9	−399.6	$^1J_{PP}$(bridge—three-membered ring)
J_{BC}	−378.7	−355.1	−315.1	
J_{EF}		−370.2	−315.1	
J_{AB}		−186.2	−217.4	$^1J_{PP}$(three-membered ring—three-membered ring)
J_{AF}	−187.6	−214.1	−217.4	
J_{BF}		−192.7	−189.8	
J_{AD}		+ 56.5	+ 91.9	
J_{BD}	+ 38.6	+ 15.4	+ 28.6	$^2J_{PP}$ (apex—three-membered ring)
J_{DF}		+ 59.5	+ 28.6	
J_{CE}		+ 19.6	+194.6	
J_{CG}	− 15.3	− 18.0	+ 5.5	$^2J_{PP}$(bridge—bridge)
J_{EG}		+ 3.4	+ 5.5	
J_{AC}		+ 7.4	+ 14.1	
J_{AE}		+ 9.4	+ 14.1	
J_{BE}	− 5.2	− 5.0	− 17.5	$^2J_{PP}$(bridge—three-membered ring)
J_{BG}		− 7.6	+ 8.1	
J_{CF}		− 2.9	− 17.5	
J_{FG}		+ 9.3	+ 8.1	



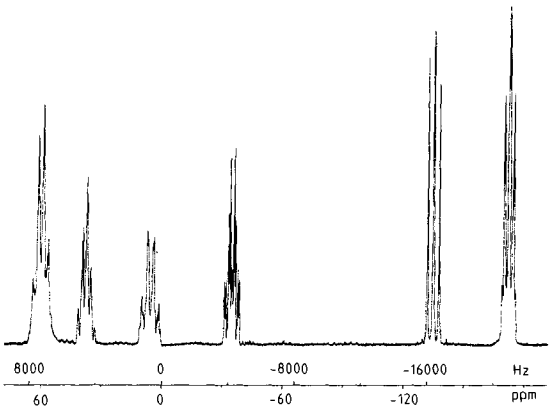


Fig. 4. ^{31}P-NMR spectrum of Li_2P_{16} in dimethylformamide (saturated) at 243 K (121.497 MHz).

3.3. Lithium Tetrahydrogen Cyclopentaphosphide, Lithium Trihydrogen Diphosphide, and Lithium Tetrahydrogen Triphosphide

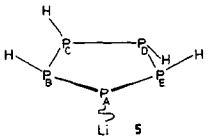
In the low-temperature metalation of **3** with *n*BuLi or $LiPH_2$ (−70 °C), the first reaction product that can be detected by ^{31}P-NMR spectroscopy is lithium tetrahydrogen cyclopentaphosphide **15**[52]. Its formation undoubtedly takes place in a rapid series of metalation and disproportionation reactions in which the highly reactive monolithiated chain-type phosphanes LiP_nH_{n+1} are first formed, which cannot exist in the presence of **3**. As in the case of the hydrides, when the chain length is $n=5$ cyclization to the thermodynamically more favorable five-membered ring compound takes place.

$$\underset{\mathbf{11}}{LiH_3P_2} \xrightarrow[-PH_3]{+P_2H_4} \underset{\mathbf{12}}{LiH_4P_3} \xrightarrow[-PH_3]{+P_2H_4} LiH_5P_4 \xrightarrow[-PH_3]{+P_2H_4} LiH_6P_5$$

$$\underset{\mathbf{3}}{LiH_6P_5} + P_2H_4 \rightarrow \underset{\mathbf{15}}{LiH_4P_5} + 2\,PH_3$$

15 can be obtained pure in solution, and by analysis of the ^{31}P{^{1}H}-NMR spectrum it has been clearly characterized as the monolithium salt of pentaphosphane(5) **5** (Table 7)[52].

Table 7. ^{31}P-NMR parameters of LiH_4P_5 in tetrahydrofuran (saturated) at 203 K; J in Hz.



5

$\delta_A = -101.9$	$J_{AB} = -360.8$
$\delta_B = -\ 7.4$	$J_{AE} = -352.0$
$\delta_C = -\ 79.3$	$J_{BC} = -240.3$
$\delta_D = -\ 50.6$	$J_{CD} = -237.4$
$\delta_E = +\ 15.7$	$J_{DE} = -219.6$
	$J_{AC} = +\ 5.5$
	$J_{AD} = +\ 12.8$
	$J_{BD} = +\ 25.9$
	$J_{BE} = +\ 80.0$
	$J_{CE} = +\ 3.9$

Above −30 °C **15** disproportionates to form **14**, for which the marked stability of the tricyclic P_7 skeleton is responsible.

$$\underset{\mathbf{15}}{2\,LiH_4P_5} \rightarrow \underset{\mathbf{14}}{Li_2HP_7} + P_2H_4 + PH_3$$

If further amounts of the metalation agent are added to the reaction system, also small quantities of lithium trihydrogen diphosphide **11** ($\delta_A = -167.0$, $\delta_B = -271.7$, $J_{AB} = -205.3$ Hz) and lithium tetrahydrogen triphosphide **12** ($\delta_A = -123.0$, $\delta_B = -251.7$, $J_{AB} = -266.8$ Hz; all at 203 K) are detectable by ^{31}P-NMR spectroscopy[52].

$\underset{\mathbf{11}}{H_2P_A—P_BHLi}$ $\qquad$ $\underset{\mathbf{12}}{H_2P_A—P_B(Li)—P_AH_2}$

4. Homocyclic Phosphorus Three-Membered Ring Compounds

Ever since the mass-spectrometric detection of the existence of triphosphane(3)[3a] as the first member of the

monocyclic phosphane series P_nH_n, the synthesis of isolable compounds with a phosphorus three-membered ring skeleton has become a challenge for preparative nonmetal chemistry. Although P_3H_3 can be separated in small amounts from phosphane mixtures by gas chromatography[53], its preparation on a preparative scale is made difficult by the extremely high rate of rearrangement into the five-membered ring compound **5**. However, since the reactivity of phosphorus hydrides can generally be reduced by suitable substitution of the hydrogens, the possibility of synthesizing relatively stable triorganocyclotriphosphanes $(PR)_3$ did not seem to be excluded.

The first derivative of P_3H_3, the pentafluoroethyl compound **18**, was described by *Cowley et al.*[54a] in 1970. In the reaction of the diiodophosphane **19** with mercury a mixture of the corresponding cyclotriphosphane and cyclotetraphosphane was obtained, which could be separated by fractional condensation. **18** was then identified by mass spectrometry and by gas density-molecular weight determination.

$$\underset{\mathbf{19}}{C_2F_5PI_2} \xrightarrow{Hg} \underset{\mathbf{18}}{(PC_2F_5)_3} + (PC_2F_5)_4$$

However, a little later *West et al.*[54b] reported that in the reaction taking place the five-membered ring compound $(PC_2F_5)_5$ was produced in place of **18**. This controversy persisted for over half a decade, until in 1976 *Mills et al.*[54c] were able to ascertain the identity of **18** by ^{31}P-NMR spectroscopy.

At the same time and independently, our Cologne group succeeded after prolonged efforts[55] in synthesizing the phenyl compound **20**, whose formation during the cyclocondensation of the diphosphane **21**[56] with phenyldichlorophosphane was unambiguously demonstrated by ^{31}P-NMR spectroscopy[57]. However, **20** cannot be isolated in the pure state, since even in solution and below room temperature it transforms relatively rapidly *via* the cyclotetraphosphane **22** into the thermodynamically stable five-membered ring compound **23**.

$$\underset{\mathbf{21}}{Me_3Si(Ph)P{-}P(Ph)SiMe_3} + PhPCl_2 \xrightarrow[-2\,Me_3SiCl]{} \underset{\mathbf{20}}{(PPh)_3}$$

$$\xrightarrow{o} \underset{\mathbf{22}}{(PPh)_4} \xrightarrow{o} \underset{\mathbf{23}}{(PPh)_5}$$

4.1. Syntheses

It has been shown in recent years that triorganocyclotriphosphanes may have considerable kinetic stability, depending on the substituent R on the three-membered ring, so that they are formed in various reactions and can often be isolated in the pure state[3c].

A general route for the generation of a phosphorus three-membered ring skeleton is the [2+1]-cyclocondensation of a bifunctional 1,2-diorganodiphosphane with an organodihalophosphane. This reaction path leads to uniformly or mixed-substituted cyclotriphosphanes.

$$X(R^1)P{-}P(R^1)X + R^2PY_2 \xrightarrow[-2XY]{} (PR^1)_2PR^2$$

Up to now the following possibilities have been verified: a) for $X=SiMe_3$, $Y=Cl$: $R^1=R^2=Ph$[57]; $R^1=Ph$, $R^2=Et$[57b]; $R^1=Ph$, $R^2=Me$[57b]; $R^1=Ph$, $R^2=iPr$[58]; $R^1=Ph$, $R^2=iBu$[58]; b) for $X=K$, $Y=Cl$: $R^1=R^2=tBu$[59]; $R^1=Ph$, $R^2=iPr$[58]; $R^1=tBu$, $R^2=iPr$[60].

A comparison of the leaving groups X on the diphosphane shows that the formation of potassium chloride generally takes place already at considerably lower temperatures than does the cleavage of chloro(trimethyl)silane. The latter is sterically hindered, particularly with bulky substituents R^1, and can thus be achieved only above 0 °C or room temperature, which is a disadvantage for the generation of thermally labile cyclotriphosphanes. On the other hand, the basic phosphide attacks the already-formed three-membered ring compound and favors a rearrangement into the comparatively more stable cyclotetra- and cyclopentaphosphanes. Thus, the cyclocondensation of the salts can only be successfully achieved in practice if the action of the educt on the reaction product is prevented by carrying out the reaction heterogeneously in a nonpolar solvent.

A synthetic route for cyclotriphosphanes that is nonspecific for the size of the ring is the dehalogenation of an organodihalophosphane by a metal.

$$RPX_2 + M^{II}(2\,M^I) \rightarrow \frac{1}{n}(PR)_n + M^{II}X_2(2\,M^IX)$$
$$n=3,\ 4,\ 5$$

The same reaction has long been used for the preparation of organo cyclophosphanes with $n>3$[1]. Thus, it is only preparatively efficient for cyclotriphosphanes when these possess a considerable stability and show an appreciable tendency to form. This is the case for $R=C_2F_5$[54a], *t*Bu[61,59], *s*Bu[62], *i*Pr[62], *c*Hex[63], and iC_3F_7[64]. In spite of this, one always obtains a mixture of oligomers of various ring sizes, which has to be separated by fractional distillation or crystallization[61-64]. However, this process is particularly suitable for making kinetically stable cyclotriphosphanes on a preparative scale.

Not significant from the preparative standpoint, but interesting on systematic grounds, is the cyclization of 1,3-dihalo-1,2,3-tri-*tert*-butyltriphosphanes **24** which have recently become available[65] to the *tert*-butyl compound **25**[66]. This reaction corresponds fully to the classical synthesis of cyclopropanes by dehalogenation of 1,3-dihalogenpropanes; the use of lithium hydride instead of a metal is advantageous, merely because of the temperature-sensitivity of **24**.

$$\underset{\mathbf{24},\ X=Hal}{X(tBu)P{-}P(tBu){-}P(tBu)X} + 2\,LiH \rightarrow \underset{\mathbf{25}}{(PtBu)_3} + 2\,LiX + H_2$$

Surprisingly, the cyclohexyl compound **26** is obtained in good yield by the action of carbon disulfide on the corresponding tetraphosphide **27**. The first step in this complex

reaction is very probably the insertion of a CS_2 molecule into the metal-phosphorus bond.

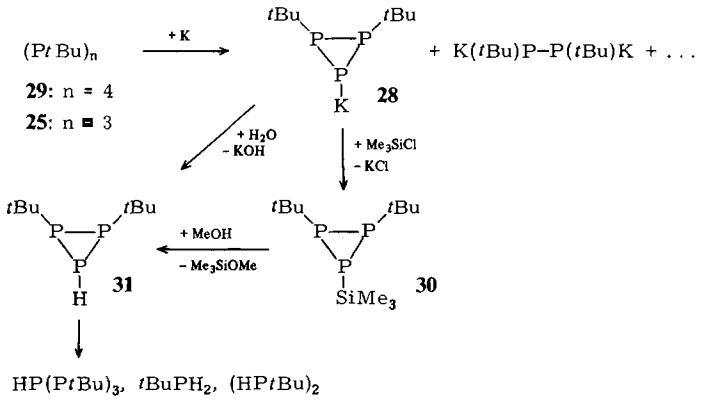
$$\underset{\mathbf{27}}{K(c\text{Hex})P\text{—}(Pc\text{Hex})_2\text{—}P(c\text{Hex})K} \xrightarrow{CS_2} \underset{\mathbf{26}}{(Pc\text{Hex})_3} + (Pc\text{Hex})_4 + \cdots$$

Finally, triorganocyclotriphosphanes are also formed in the thermolysis of cyclophosphanes with $n > 3$, as has been demonstrated for R = Et[57a,67] and for R = Me[20a,68].

$$(PR)_5 \xrightarrow{\Delta} (PR)_3 + (PR)_4 + (PR)_6 + \cdots$$

In agreement with the known stabilization of small ring systems by bulky substituents, it has been possible so far to isolate in pure form the uniformly and mixed-substituted cyclotriphosphanes $(Pt\text{Bu})_3$[59,61], $(Ps\text{Bu})_3$[62], $(Pi\text{Pr})_3$[62], $(Pc\text{Hex})_3$[63], $(PiC_3F_7)_3$[64] and $(Pt\text{Bu})_2(Pi\text{Pr})$[60], all as compounds stable at room temperature.

Of particular interest as a synthon is the monometalated cyclotriphosphane **28**. This is formed—together with other open-chain and cyclic *tert*-butyl phosphides—in the ring cleavage of the cyclophosphanes **29**[69] or **25**[70] with potassium. By direct protolysis or—which is better from the preparative standpoint—*via* the silyl derivative **30**, earlier obtained by *Fritz et al.*[71] in another way, this compound can be converted into the partially hydrogen-substituted cyclotriphosphane **31**[70]. Compared with **25**, **31** is kinetically destabilized and even below room temperature a rearrangement takes place to form the four-membered ring compound **32**, with simultaneous partial decomposition.



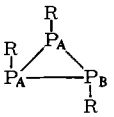
4.2. Properties and Structural Characteristics of Triorganocyclotriphosphanes

The triorganocyclotriphosphanes made on the preparative scale up to now are colorless, somewhat viscous liquids or crystalline solids oxidizing easily in air. They are readily to very readily soluble in ethers and in aliphatic and aromatic hydrocarbons, polar solvents favoring the rearrangement into cyclophosphanes with $n > 3$. Decomposition takes place with halogenated hydrocarbons.

All cyclotriphosphanes are characterized in their $^{31}P\{^1H\}$-NMR spectra by chemical shifts at high fields compared to open-chain triphosphanes or to cyclophosphanes of other ring sizes[72]. Accordingly, the $\delta(^{31}P)$ values are influenced by the three-membered ring structure in the same direction as the $\delta(^{31}C)$ values of the cyclopropanes[73]. The even more marked "small ring effect" observed with phosphorus compounds can be attributed to the predominant s-character, and the consequently enhanced shielding effect of the free electron pairs on the phosphorus atoms of the cyclotriphosphanes[57b].

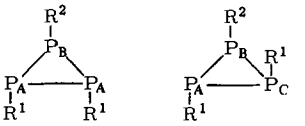
The uniformly substituted cyclotriphosphanes $(PR)_3$ show in each case an A_2B spin system (Table 8), which means that the substituents are undoubtedly arranged on both sides of the ring plane. More precisely, the $\delta(^{31}P)$ values are determined not only by the endocyclic bond angles but also by the exocyclic angles, the dihedral angle between the free electron pairs of adjacent P atoms, and the β-effect[20a].

Table 8. ^{31}P-NMR parameters of the cyclotriphosphanes $(PR)_3$; J in Hz.



R	δ_A	δ_B	J_{AB}	Ref.
Me	−171.0	−157.3	−170.8	[68]
Et	−157.3	−145.0	−178.5	[67]
*c*Hex	−141.7	−138.9	−185.0	[63]
*i*Pr	−132.3	−128.6	−184.8	[62]
Ph	−131.7	−147.2	−186.9	[57]
*t*Bu	− 71.9	−108.1	−201.1	[61]

Table 9. ^{31}P-NMR parameters of the cyclotriphosphanes $(PR^1)_2PR^2$; J in Hz.



a (A_2B) **b** (ABC)

R^1	R^2		δ_A	δ_B	δ_C	J_{AB}	J_{AC}	J_{BC}	Ref.
*t*Bu	*i*Pr	a	− 68.5	−127.8		−192.1			[60]
		b	−109.0	−112.5	− 99.5	−188.7	−205.1	−262.2	
Ph	*t*Bu	a	−137.4	−162.9		−185.6			[58]
		b	−149.9	−148.7	−140.9	−180.0	−195.3	−216.0	
Ph	*i*Pr	a	−140.3	−134.1		−189.9			[58]
		b	−152.3	−123.6	−136.9	−185.3	−184.1	−226.9	
Ph	Et	a	−138.7	−151.8		−186.3			[57b]
		b	−148.3	−141.6	−138.8	−182.7	−184.8	−220.0	

The configuration of the triorganocyclotriphosphanes has been confirmed by crystal structure analysis of the *tert*-butyl compound **25**[74]. Figure 5 shows the arrangement of the substituents of the two independent molecules in the crystal association.

In the mixed-substituted cyclotriphosphanes $(PR^1)_2PR^2$ there are two diastereomers. The symmetric isomer **a** with identical substituents on one side of the ring shows an A_2B system in the $^{31}P\{^1H\}$-NMR spectrum, and the asymmetric isomer **b** an ABC system (Table 9). If R^1 and R^2 are not

bulky groups, both isomers will be formed in the statistical ratio of **a** : **b** = 1 : 2[3c].

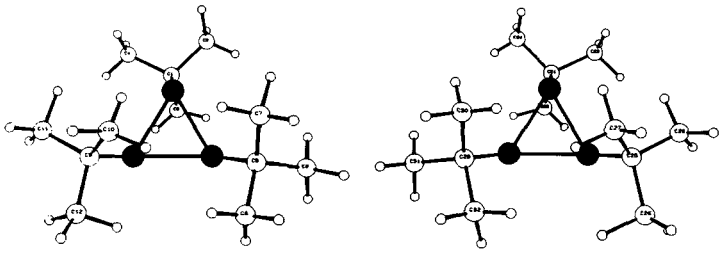


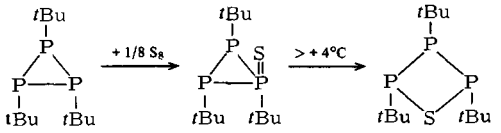
Fig. 5. Structure of the two independent molecules of $(PtBu)_3$ in the crystal [74].

4.3. Reactions of Triorganocyclotriphosphanes

Insofar as the reaction behavior of triorganocyclotriphosphanes is known at all, one can distinguish between reactions in which the P_3 ring skeleton is preserved and ones in which it is changed.

4.3.1. Reactions in which the P_3 Ring Skeleton is Preserved

As a rule, additions on the λ^3 phosphorus in cyclotriphosphanes proceed with opening of the three-membered ring structure. However, it has proved possible to make the monothiocyclotriphosphane **33** by the action of sulfur on the *tert*-butyl compound **25** under mild reaction conditions, and to enrich this compound up to 50 mol-% in the reaction mixture[75]. The compound is thermally unstable and rapidly rearranges at room temperature into the heterocyclic four-membered ring compound **34**[75].



25 **33** **34**

Trivalent phosphorus compounds are generally outstanding ligands in the chemistry of complexes. Thus, cyclotriphosphanes react as expected with metal carbonyls, to form mononuclear and binuclear cyclotriphosphanecarbonylmetal complexes (**35** and **36**), which are remarkably stable both thermally and to oxidation[76] (Fig. 6[77]). The P_3 ring here functions—as in hexamethyltetraphosphatrisilanortricyclene[78] but differently from the triphenylcyclotriphosphane complex **37** obtained in another way[79]—as a 2- or a 4-electron donor[80].

$(PR)_3M(CO)_5$	$(PR)_3[M(CO)_5]_2$	$(PPh)_3[Mn(CO)_2Cp]_3$
35	**36**	**37**
$R = iPr$; $M = Cr$, *Mo*, W	$R = iPr$; $M = Cr$, W	
$R = tBu$; $M = Cr$, W		

4.3.2. Reactions in which the P_3 Ring Skeleton is Changed

Triorganocyclotriphosphanes are only metastable in comparison with the corresponding cyclophosphanes with $n > 3$. Thus, depending on the substituents R and the polarity of the solvent, they undergo rearrangements at various rates to form the stable four-membered or five-membered ring phosphanes[82]. The individual reaction steps do

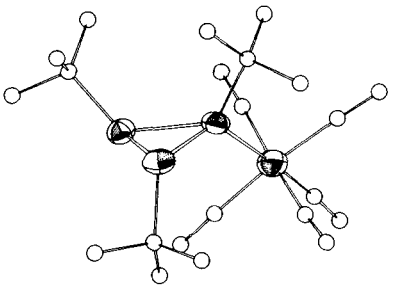


Fig. 6. Structure of $(PtBu)_3Cr(CO)_5$ [77].

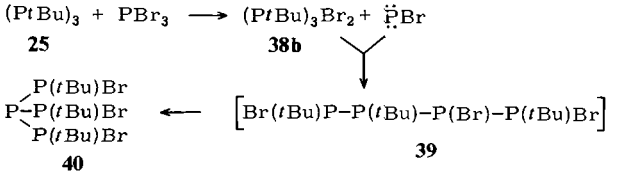
not proceed radically *via* free phosphinidenes $\ddot{P}R$, but rather, most probably, by a four-center mechanism between two P—P groups[57b,60], as has also been assumed for the formation of the mixed-substituted cyclopentaphosphanes[83]. The corresponding transition state requires a *trans* arrangement of the free electron pairs on the phosphorus atoms of the participating P—P bonds. The resultant dimerization which takes place first leads to a six-membered ring compound, which is not, however, observed to be the main rearrangement product of the cyclotriphosphanes. Enrichment of this species is opposed by its comparatively high reactivity, which is a result of the conformational mobility and hence the ability of the free electron pairs on adjacent P atoms to assume a *trans* position. The same is true of cyclophosphanes with $n > 6$. Thus, subsequent reactions first produce still larger rings, such as cyclonona- and perhaps also cyclododecaphosphanes, which then break up again into smaller oligomers. In the course of these rearrangements there is a progressive enrichment of the thermodynamically favored four-membered or five-membered ring compounds[82].

Mild halogenation of the *tert*-butyl compound **25** leads to 1,3-dihalo-1,2,3-triorganotriphosphanes **38**, which are of considerable interest as synthetic reagents for the preparation of new open-chain and ring-type *tert*-butylphosphanes[65]. **38a** is a remarkably stable open-chain triphosphane.

$$(PtBu)_3 + X_2 \rightarrow X(tBu)P{-}P(tBu){-}P(tBu)X$$

25 — **38a**: X = Cl; **38b**: X = Br; **38c**: X = I

If phosphorus(III) bromide is used for ring-opening with halogenation, the subsequent reaction consists in the insertion of the intermediate bromophosphanediyl into **38b** with the formation of the mixed-substituted tetraphos-



phane **39**. As expected, the latter is unstable and rearranges to form the constitutional isomer **40**[84].

The light-sensitive compound **40** is the first derivative of isotetraphosphane(6) that is stable at room temperature in the absence of air[85] (see Section 2.2).

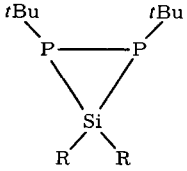
5. Heterocyclic Phosphorus Three-Membered Ring Compounds of the Types $(PR^1)_2ER^2_n$ and $(PR)_4E$

Three-membered ring compounds with only one phosphorus atom in the ring have been known since the work of *Goldwhite et al.*[88] in the 'sixties and have already been reviewed in recent times[89]. In contrast, three-membered phosphorus heterocycles with two P atoms have generally been thought to be extremely reactive and hence not preparatively accessible because of the thermal instability of heterocyclopropanes with elements of the second short period[90]. However, in recent years it has become possible to make a broad spectrum of three-membered ring heterocyclophosphanes with carbon, silicon, germanium, tin, boron, nitrogen, arsenic, antimony, sulfur, and selenium as the heteroatoms, and in large part also to isolate them in the pure state[3c,d,91].

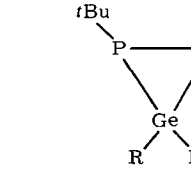
A suitable route for the generation of a P_2E ring skeleton (E = heteroatom) is the [2+1]-cyclocondensation of a bifunctional 1,2-diorganodiphosphane with a geminal nonmetal or metal compound. Assuming, that the leaving groups on the phosphorus and on the heteroatom will all cause the requisite polarization of the remainder of the molecule and will combine to form a stable leaving compound, this reaction has a very broad field of application. The *tert*-butyl-substituted diphosphanes **41**[69] and **42**[92] are particularly well suited synthetic reagents for the preparation of kinetically stable phosphorus three-membered ring heterocycles.

$$X(R^1)P{-}P(R^1)X + R^2_nEY_2 \xrightarrow[-2XY]{} (PR^1)_2ER^2_n$$

X = K, Y = Cl : E = C, Si, Ge, Sn, B, As, Sb
X = Cl, Y = Me_3Sn : E = S, Se, N



41

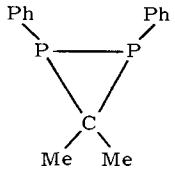


42

5.1. Diphosphiranes (Diphosphacyclopropanes)

Among the three-membered ring heterocyclophosphanes the diphosphiranes are of particular interest. Their successful synthesis completes an unbroken transition in the series of three-membered ring compounds from cyclopropane to cyclotriphosphane.

The first spectroscopic detection of the diphosphirane **43**[93] stimulated efforts to synthesize kinetically more stable representatives. The reactions of **41** with dichloromethane, 1,1-dichloroethane, or 2,2-dichloropropane give the diphosphiranes **44a—c**, which can be isolated by distillation as oxidation-sensitive liquids[94a,b]. While **44c** is surprisingly stable in the absence of air, and can even be heated to 200 °C for a short time without decomposition, **44a** dimerizes already quantitatively to **45** within a few days at room temperature. With 1,1-dichloroolefins the



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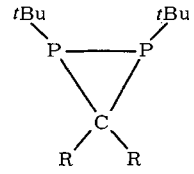
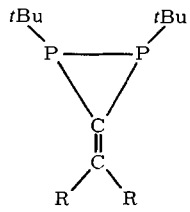
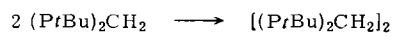


44a: R = H
44b: R = H, Me
44c: R = Me



46a: R = H
46b: R = Me
46c: R = 4-ClC$_6$H$_4$



44a **45**

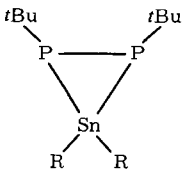
methylenediphosphiranes **46a—c** are formed, but because of their enhanced reactivity only **46b** and **46c** can be prepared in the pure state[3c,95]. The diphosphirane structure of all these compounds is ascertained unambiguously from the high-field position of their ^{31}P-NMR signals, which occur in the cyclotriphosphane region (see Table 10).

5.2. Diphosphasiliranes, Diphosphagermiranes, and Diphosphastanniranes

The reactions of **41** with diorganodichlorosilanes, diorganodichlorogermanes, and diorganodichlorostannanes lead to the heterocyclic compounds **47—49**[3c,d,96,97]. The reactivity of the compounds increases with increasing covalent radius of the heteroatom and with decreasing bulk of its substituents. Thus, the diphosphasilirane **47a** is appreciably less stable than the diphosphirane **44c**, and the diphosphastannirane skeleton can only be stabilized sufficiently by *tert*-butyl groups on the tin atom, while with smaller substituents dimerization takes place at once.

47a: R = Me
47b: R = Ph

48a: R = Et
48b: R = Ph



49: R = *t*Bu

As has been shown by the investigation of the crystal structure of **47b**[98], the replacement of a $>PtBu$ ring member in the cyclotriphosphane **25** by a $>SiPh_2$ group leads

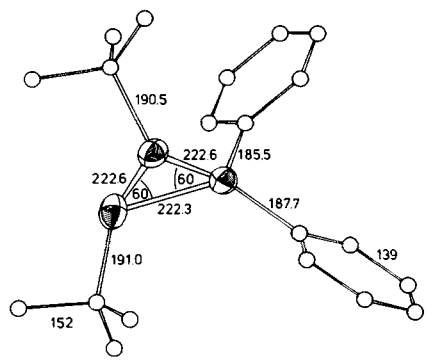


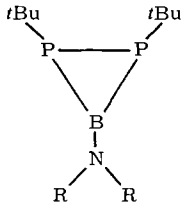
Fig. 7. Structure of $(PtBu)_2SiPh_2$ [98].

to little if any distortion of the ring skeleton, so that the endocyclic bond angle at the phosphorus and silicon is in each case 60° (Fig. 7). This is surprising, since silicon generally shows a considerably greater tendency than phosphorus to keep the tetrahedral angle constant.

In diphosphagermirane **48a** the greater covalent radius of the germanium atom compared to phosphorus results in a reduction of the interior ring angle at the heteroatom to 58°, but the deviations compared to an equilateral three-membered ring are not large[3c, 99].

5.3. Diphosphaboriranes

41 reacts with diorganoaminodichloroboranes to give the diphosphaboriranes **50a—50g**, while with organodihaloboranes only larger phosphorus-boron rings are produced[100].



50a: R = Et
50b: R = *i*Pr
50c: R = Me, *n*Bu
50d: R = Me, *t*Bu
50e: R = Me, *c*Hex
50f: R = Me, Ph
50g: R = Ph

The P_2B heterocycles are stable at room temperature if the substituent on the boron contains two secondary C-atoms or one primary and one tertiary C-atom in α position to the nitrogen (**50b** and **50d**). If both of the alkyl groups are unbranched (**50a** and **50c**), or if the electron density on the nitrogen is lowered by phenyl substitution (**50f** and **50g**), dimerization will take place relatively rapidly. The occurrence of an AB-spin system in the ^{31}P-NMR spectra of **50c—50f** indicates the presence of a partial double bond between the boron and the nitrogen atoms. In contrast, corresponding to the high-field position of the signals, there is no appreciable phosphorus-boron π interaction in the ring (see Table 10). According to the results of X-ray structure analysis carried out on **50a**, the endocyclic bond angle is 54° at the phosphorus, and 72° at the sp^2-hybridized boron (Fig. 8)[101].

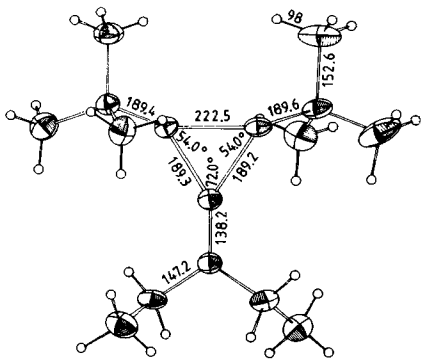
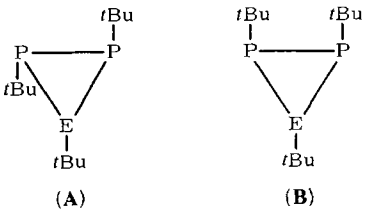


Fig. 8. Structure of $(PtBu)_2BNEt_2$ [101].

The diphosphaboriranes are at the same time the first-known monocyclic three-membered ring boron compounds, since no boracyclopropane has been known up to now.

5.4. Diphosphaarsiranes and Diphosphastibiranes

The heterocycles **51**[102] and **52**[3d, 103] obtained by reacting **41** with *tert*-butyldichloroarsane or *tert*-butyldichlorostibane are both formed as mixtures of the diastereomers **A** and **B**, of which the isomer **A**, with *trans*-oriented *tert*-butyl groups at the phosphorus atoms, is more stable. While **51** can be isolated in the form of colorless, light-sensitive crystals, **52** rearranges already at −78 °C into larger phosphorus-antimony rings.

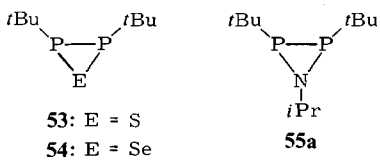


51: E = As
52: E = Sb

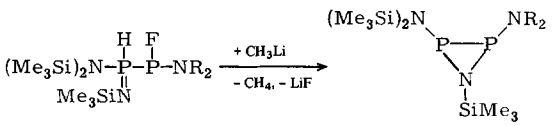
The remarkable stability of **51** also stimulated the synthesis of phosphadiarsiranes[104] and of tri-*tert*-butylcyclotriarsane[105], so that in the series of three-membered ring compounds from cyclotriphosphane to cyclotriarsane examples are known for each stage.

5.5. Thia-, Selena-, and Azadiphosphiranes

Heterocyclic phosphorus three-membered ring compounds with the electronegative ring members sulfur, selenium, and nitrogen have been obtained by the condensation of the diphosphane **42** with the stannyl compounds of the corresponding elements[106, 107]. The thiadiphosphirane **53** is also produced in the thermolytic ring contraction of larger phosphorus-sulfur heterocycles, and in the reaction of sulfur dichloride with 1,2-di-*tert*-butyldiphosphane or with the diphosphasilirane **47b**[106]. Azadiphosphiranes with bulky amino groups on the phosphorus have been prepared by *Niecke et al.*[108], by the dehydrohalogenation of a phosphorane with a P—P bond.



53: E = S
54: E = Se
55a



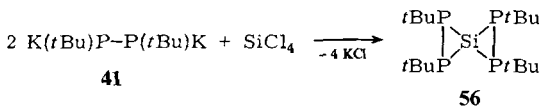
55b: R = $SiMe_3$
55c: R = $CHMe_2$

Collectively, these heterocyclic compounds can be isolated by distillation and show considerable kinetic stability. In contrast to the aziridines, the appearance of their $^{31}P\{^1H\}$-NMR spectra down to −140 °C is not temperature-dependent, so that the nitrogen has a planar surrounding, most probably because of the formation of dative π-bonds to the phosphorus atom.

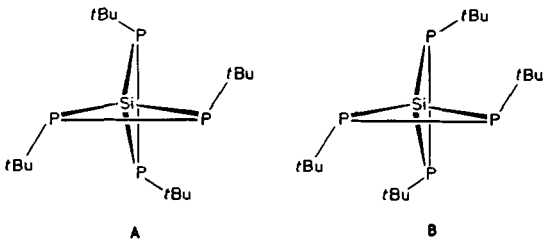
5.6. A Spirocyclic Phosphorus Three-Membered Ring Compound

As early as in 1896 it had proved possible to link two cyclopropane rings at a common carbon atom to form spiro[2.2]pentane[109]. It was therefore a challenge for preparative chemists to combine two P_2E rings at the common heteroatom E into a spirocyclic compound.

The synthesis of the tetraphosphasilaspiro[2.2]pentane **56** could be recently achieved in our group by cyclocondensation of silicon tetrachloride with the diphosphide **41**[110]. At the same time, **56** is the first spirocyclic compound made from two three-membered rings with silicon as the central atom.



41 **56**



The compound **56** is formed as a mixture of the isomers **A** and **B**, which can be isolated separately and which differ from each other in the relative arrangement of the *trans*-oriented *tert*-butyl groups at the two three-membered rings. The sterically less favored isomer **B** slowly rearranges at room temperature into the more stable isomer **A**. According to the results of X-ray structure analysis[111], in the individual, mutually perpendicular P_2Si rings the endocyclic bond angles at the phosphorus and silicon atoms are *ca.* 60°.

5.7. ^{31}P-NMR Parameters of the Phosphorus Three-Membered Ring Heterocycles $(PR^1)_2ER^2_n$ and $(PR)_4E$

As in the case of the homocyclic phosphorus three-membered ring compounds, so with the heterocyclic compounds the signal positions in the ^{31}P-NMR spectra are determined mainly by the size of the ring.

Table 10, which is arranged according to substance classes, illustrates the dependence of the $\delta(^{31}P)$ values on the individual heteroatoms. The dominant influence is that of the covalent radius, while the electronegativity is only of secondary significance: an increase in the P—E bond length widens the endocyclic bond angles at the phosphorus atoms and thus produces a shift in the downfield direction; at the same time, the absolute value of the negative $^1J_{PP}$ coupling constant increases. Moreover, the $\delta(^{31}P)$ values of the three-membered ring heterocycles are influenced by the same parameters as those of the homocyclic compounds.

Table 10. ^{31}P-NMR parameters of the three-membered ring phosphorus heterocycles $(PR^1)_2ER^2_n$ and $(PR)_4E$; J in Hz.

Compound		δ_A	δ_B	J_{AB}	Ref.
$(PPh)_2CMe_2$	**43**	−122			[93]
$(PtBu)_2CR_2$					
R = H	**44a**	−168.8			[94a]
R = H, Me	**44b**	−129.4	−138.5	−162.4	[94b]
R = Me	**44c**	− 91.7			[94a]
$(PtBu)_2C{=}CR_2$					
R = H	**46a**	−143.2			[3c]
R = Me	**46b**	−139.1			[3c]
R = 4-ClC_6H_4	**46c**	−149.7			[3c]
$(PtBu)_2SiR_2$					
R = Me	**47a**	−132.7			[96]
R = Ph	**47b**	−122.4			[96]
$(PtBu)_2GeR_2$					
R = Et	**48a**	−126.8			[3c]
R = Ph	**48b**	−113.3			[3c]
$(PtBu)_2SntBu_2$	**49**	− 73.3			[3d]
$(PtBu)_2BNR_2$					
R = Et	**50a**	−152.5			[100b]
R = *i*Pr	**50b**	−159.2			[100a]
R = Me, *n*Bu	**50c**	−145.7	−150.3	− 75.9	[100b]
R = Me, *t*Bu	**50d**	−139.8	−168.8	− 77.2	[100b]
R = Me, *c*Hex	**50e**	−147.3	−157.0	− 75.8	[100b]
R = Me, Ph	**50f**	−141.8	−155.4	− 79.4	[100b]
R = Ph	**50g**	−151.4			[100b]
$(PtBu)_2AstBu$	**51**				[102]
Isomer A		− 45.1	− 86.0	−230.5	
Isomer B		− 51.5			
$(PtBu)_2SbtBu$	**52**				[103]
Isomer A		− 40.0	− 69.3	−245.9	
Isomer B		− 42.5			
$(PtBu)_2S$	**53**	− 91.5			[106]
$(PtBu)_2Se$	**54**	− 76.9			[106]
$(PtBu)_2NiPr$	**55a**	− 67.0			[107]
$(PtBu)_4Si$	**56**				[111]
Isomer A		−152.3			
Isomer B		−145.1			

6. Polycyclic Organophosphanes

Phosphorus compounds with the compositions P_7R_3, P_8R_6, and P_9R_3, in which the hydrogens of polycyclic hydrides have been replaced by alkyl or phenyl groups, have already been observed several times in the thermolysis of open-chain or cyclic phosphane derivatives and identified by mass spectroscopy[40, 60, 112]. However, their isolation and structural characterization are opposed by considerable preparative difficulties. Since a better knowledge of these compounds was expected to yield the decisive key to understanding the complex structures of the polycyclic hydrides P_nH_{n-2m} ($n \geq 4$, $m = 1-7$), the Cologne group has, for some time, devoted considerable attention to this class of compounds.

6.1. Syntheses

The first polycyclic organophosphane prepared was trimethylheptaphosphane(3) **13**, obtained by the reaction of trilithium heptaphosphide **10** with methyl bromide[6, 40]. The formation of the P_n skeleton of **10** takes place—as in

the case of the polycyclic hydrides in Table 1—by uncontrolled disproportionation (see Section 3.1).

$$\underset{\textbf{10}}{Li_3P_7} + 3\,MeBr \xrightarrow[-3\,LiBr]{} \underset{\textbf{13}}{P_7Me_3}$$

The breakthrough in the production of polycyclic organophosphanes on a preparative scale came with the discovery of directed and generally applicable synthetic methods. Since organodichlorophosphanes give monocyclic phosphorus compounds on dehalogenation[1], in order to obtain polycyclic organophosphanes it is necessary to introduce into the reaction additional phosphorus atoms not substituted with organo-groups. Corresponding to this concept, substances of the general composition $P_{x+y}R_x$ can be made by any of the reaction paths (c) to (e).

$$x\,RPCl_2 + y\,PCl_3 + \frac{2x+3y}{2}\,Mg \longrightarrow P_{x+y}R_x + \frac{2x+3y}{2}\,MgCl_2 \qquad (c)$$

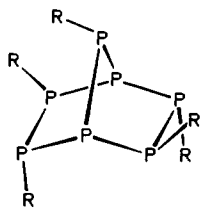
$$\frac{x}{n}(PR)_n + y\,PCl_3 + \frac{3y}{2}\,Mg \longrightarrow P_{x+y}R_x + \frac{3y}{2}\,MgCl_2 \qquad (d)$$

$$x\,RPCl_2 + \frac{y}{4}P_4 + x\,Mg \longrightarrow P_{x+y}R_x + x\,MgCl_2 \qquad (e)$$

Other dehalogenating agents, such as lithium hydride, can be used instead of magnesium[113]. In all cases the overall composition of the reaction product, *i.e.* the number of organo-substituted P atoms compared to the number of P atoms connected only to other phosphorus atoms, can be established from the molar ratio of the two starting phosphorus-containing compounds. However, whether the stoichiometry observed corresponds to a definite organophosphane or only to a mixture of substances with the same overall composition will depend on the thermodynamic and the kinetic stability of the compounds involved. Since the stoichiometric composition of various polycyclic organophosphanes can be very similar to one another, a product mixture of several compounds is always obtained which must be separated chromatographically.

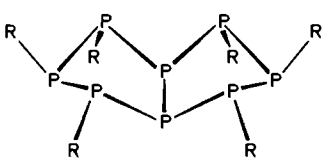
6.2. Bicyclophosphanes: P_7R_5, P_8R_6, P_6R_4

Dehalogenation in accordance with (c) or (d) at moderate temperature leads to heptaphosphanes(5)[114] or octaphosphanes(6)[115], of which **57a**, **57b**, **58b**, and **58c** have been isolated as oily liquids.



P_7R_5

57a: R = Me
57b: R = Et
57c: R = *i*Pr



P_8R_6

58a: R = Me
58b: R = Et
58c: R = *i*Pr

The structures of these compounds have been determined by NMR spectroscopy and confirmed by a complete analysis of the $^{31}P\{^1H\}$-NMR spectra of **57a**, **57b**, and **58b**[116]. According to this, the compounds **57** are 2,3,5,6,7-pentaorganobicyclo[2.2.1]heptaphosphanes with a skeleton analogous to that of norbornane, while the **58**-type compounds are 2,3,4,6,7,8-hexaorganobicyclo[3.3.0]octaphosphanes with a structure analogous to pentalane. In the case of **57a—c**, apart from the dominant configurational isomer with the maximum *trans* arrangement of the substituents other isomers occur with a lower relative frequency.

The compounds **58a—c** are always formed together with the corresponding compounds **57**, in spite of the maintenance of the required stoichiometry. This can clearly be attributed to the fact that both the octaphosphanes(6) and the heptaphosphanes(5) contain a bicyclic molecular skeleton consisting of two phosphorus five-membered rings. It follows from the product distribution in each case that with small substituents (Me, H) the P_7-skeleton with a one-atom bridge has an appreciably greater tendency to form than the P_8-skeleton with a zero bridge. With increasing bulk of the substituents (Et, *i*Pr), however, the stability difference between the two bicyclophosphane skeletons is changed, since the steric interactions of the substituents on P^6 and P^7 in **57** are considerably greater than those of the *cis* substituents in **58**, so that the **58** : **57** ratio increases.

On going over to R = *t*Bu both the norbornane and the pentalane skeletons are destabilized: while no corresponding heptaphosphane(5) has so far been obtained[117], the relatively stable octaphosphane(6) shows the unusual structure of a 2,2',3,3',4,4'-hexa-*tert*-butyl-1,1'-bicyclotetraphosphane **59**[118] (Fig. 9). All the P—P bond lengths within the nonplanar four-membered rings and in the bridge are approximately the same. Rotation around the exocyclic P—P bond is already frozen-in at room temperature[119]. The mixed bicyclic compound $P_6As_2tBu_6$ **60**, accessible according to reaction (c) with arsenic trichloride instead of phosphorus trichloride, has the same structure, with arsenic atoms in the bridgehead positions[120].

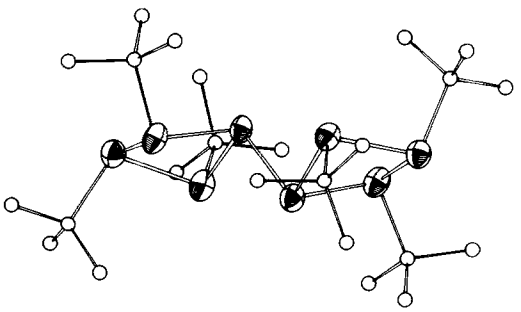


Fig. 9. Structure of P_8tBu_6.

Together with **59**, a further bicyclic compound, namely a hexaphosphane(4), is produced in accordance with reaction (c) in a wide range of mixture ratios of *tert*-butyl dichlorophosphane and PCl_3; surprisingly, this compound has a phosphorus skeleton comprising a three-membered ring and a five-membered ring. It is therefore a 2,3,4,6-tetra-*tert*-butylbicyclo[3.1.0]hexaphosphane **61**[121a,b] (Fig.

10). The slightly distorted three-membered ring is nearly perpendicular to the relatively flat five-membered ring. In spite of this unusual structure, **61** is remarkably stable toward heat and atmospheric oxygen.

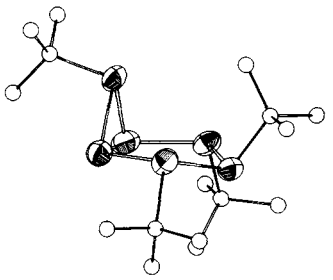
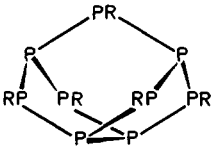


Fig. 10. Structure of P_6tBu_4.

6.3. Tricyclophosphanes: P_7R_3, P_9R_5

If the dehalogenation according to reaction (d) is carried out at an elevated temperature (boiling tetrahydrofuran), then in addition to phosphorus-richer polycyclics the heptaphosphanes(3) with R = Me, Et, *i*Pr are preferentially formed[122]. The methyl compound **13** is identical with the reaction product obtained from **10** and methyl bromide in all its properties, including the distribution of the isomers[6,40]. The compounds are 3,5,7-triorganotricyclo-[2.2.1.$0^{2,6}$]heptaphosphanes, with a skeleton analogous to that of nortricyclene (see Section 3.1), as has been ascertained by a complete analysis of the $^{31}P\{^1H\}$-NMR spectra of the two configurational isomers of **13**[123].

Under suitable conditions of stoichiometry, reaction temperature, and reaction time, nonaphosphanes(5) are formed predominantly according to reactions (c) or (d), of which the compounds **62a** and **62b** have been isolated as analytically pure, high-viscosity oils[114,124].



P_9R_5

62a: R = Me
62b: R = Et
62c: R = *i*Pr

Their structure has been clearly shown from the $^{31}P\{^1H\}$-NMR spectra to be 2,4,6,8,9-pentaorganotricyclo[3.3.1.$0^{3,7}$]nonaphosphanes with a P_9 skeleton analogous to that of noradamantane. Since the >PR ring members in these molecules are all separated from one another by unsubstituted P atoms, a deviation from the all-*trans* arrangement of the substituents does not lead to any drastic destabilization. As a result, in all cases mixtures of various configurational isomers with comparable frequency are formed (*e.g.* **62a**: 3 isomers in the ratio 40:40:20); this constitutes the reason for the low tendency of these compounds to crystallize.

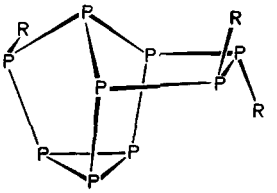
Furthermore, a constitutional isomer of **62b** is formed in accordance with reaction (e), and has been separated in the pure form[125]. Since its $^{31}P\{^1H\}$-NMR spectrum shows no signal groups in the three-membered or four-membered ring region, the P_9 skeleton should have a structure analogous to the hydrocarbons brendane or brexane. A definitive clarification of this question is difficult, because the spectrum is extremely complex owing to the presence of configurational isomers.

6.4. Tetracyclophosphanes: P_9R_3, $P_{11}R_5$

Of the phosphorus hydrides with nine P atoms, nonaphosphane(3) is outstanding because of its marked stability and tendency towards formation[3b]. In agreement with this, organo-substituted nonaphosphanes(3) are generally formed in the thermolysis of open-chain or ring-type phosphane derivatives[40,60,112,121a].

According to reaction (c) considerable portions of nonaphosphanes(3) are produced under suitable reaction conditions (excess of PCl_3, prolonged reaction time at elevated temperatures), often together with corresponding heptaphosphanes(3)[126]. Separation of the product mixture is difficult owing to the poor solubilities, but has recently been achieved in the case of the *tert*-butyl compound **63d**.

63a: R = Me
63b: R = Et
63c: R = *i*Pr
63d: R = *t*Bu



P_9R_3

According to data from the $^{31}P\{^1H\}$-NMR spectra of **63b** and **63d**, these compounds are 5,8,9-triorganotetracyclo[4.3.0.$0^{2,4}$.$0^{3,7}$]nonaphosphanes with a P_9 skeleton analogous to that of the hydrocarbon deltacyclane. Corresponding to the observed nonequivalence of all nine P-atoms, the symmetry is of the C_1 type, while the symmetric triasterane structure assumed by other authors[38,112] is inconsistent with the spectroscopic findings. As expected, there are two configurational isomers of different frequencies, which differ in their spatial arrangements of the substituent on P^5. The deltacyclane skeleton is also present as a structural element in the P_{16}^{2-} ion (see Section 3.2).

Together with the tricyclic nonaphosphanes(5), varying amounts of the corresponding undecaphosphanes(5) are formed in most cases[114,125]. This suggests that the stabilities of the two classes of compounds are similar and that their structures are closely related. In agreement with this, the results so far obtained on enriched $P_{11}Et_5$[125] suggest that the structure is associated with the noradamantane (or brendane or brexane) analogous $P_9(5)$ skeleton in a similar manner as the $P_9(3)$ skeleton is associated with the $P_7(3)$ skeleton, namely by an additional two-atom bridge, giving a new five-membered ring.

6.5. General Properties of Polycyclic Organophosphanes

The polycyclic organophosphanes so far obtained on a preparative scale are colorless to yellow oily liquids or solids, which only crystallize when they do not consist of diastereomeric mixtures. Their solubilities in the usual solvents become lower with increasing number of phosphorus atoms and decreasing number of organo groups. Within a

given class of compounds, the solubility increases with increasing number of C-atoms in the substituents. In the ethyl, and particularly methyl, compounds there is often a marked reduction of the solubility on allowing the solution to stand or after complete removal of the solvent. This physical aggregation process, which is limited to small substituents and which is still unexplained, is also responsible for the extremely sparing solubility of the underlying polycyclic phosphorus hydrides. The stability of the organophosphanes to atmospheric oxygen increases with increasing phosphorus content and with increasing bulk of the substituents.

7. General Structural Principles of Polycyclic Phosphanes and their Derivatives

The structures established for the organophosphanes with condensed ring systems constitute an essential key to understanding the structures of the polycyclic phosphorus hydrides, which because of their low solubilities and poor crystallizability have not yet proved amenable to NMR or X-ray investigation. As shown by the synopsis in Figure 11, a variation of the substituents in the range of relatively small alkyl groups brings about no alteration of the phosphorus skeleton, so that even when the organo groups have been replaced by hydrogens a structural change can be reliably excluded. This leads to definitive conclusions for a whole range of phosphorus hydrides:

P_7H_5 is a bicyclo[2.2.1]heptaphosphane;
P_7H_3 is a tricyclo[2.2.1.$0^{2,6}$]heptaphosphane;
P_8H_6 is a bicyclo[3.3.0]octaphosphane;
P_9H_5 is a tricyclo[3.3.1.$0^{3,7}$]nonaphosphane;
P_9H_3 is a tetracyclo[4.3.0.$0^{2,4}$.$0^{3,7}$]nonaphosphane.

Small differences between the hydrogen- and the methyl-substituted phosphanes are only expected in the frequency distribution of the various configurational isomers, since with trimethylheptaphosphane(3) **13** there is already a sterically determined deviation from the statistical distribution (see Section 3.1).

Significant changes in the skeleton structures characteristic for the individual compound classes—as in the case of P_8tBu_6 **59**—may be compelled by special steric conditions; however, these only represent nature's emergency measure, as shown by the fact that the element-homologous compound As_8tBu_6 has the same structure as the sterically unhindered octaphosphanes(6)[118a, 127]. Whether the unusual skeleton in P_6tBu_4 is only limited to bulky substituents will be shown by further investigation of the compounds P_6R_4 (R = Et[124], Me[117], H[3b]) already identified by mass spectroscopy. In general, the formation of different skeleton structures within one and the same class of compounds should mainly be reckoned with in the bicyclophosphanes, where steric interactions between the substituents play a far greater role than in tri-, tetra- or pentacyclic compounds.

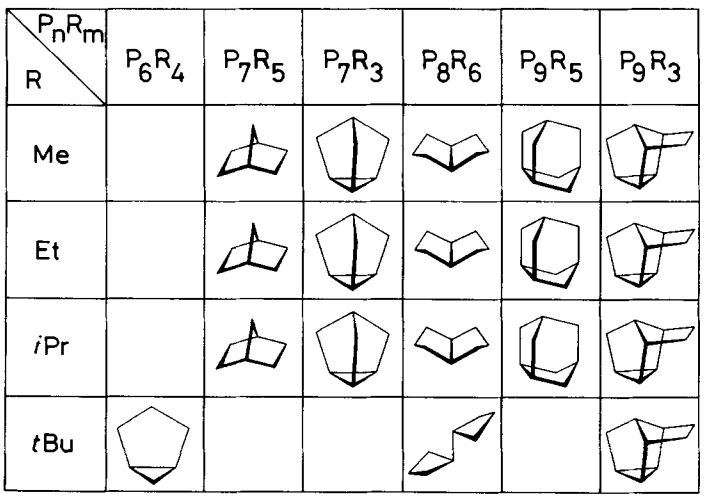


Fig. 11. Phosphorus skeleton in polycyclic organophosphanes.

The P_n skeletons of the various classes of compounds show close family relationships. For example, the double ring in P_6tBu_4 can be obtained formally from the tricyclic $P_7(3)$ cage if one of the three one-atom bridges is removed. The $P_7(5)$ skeleton analogous to norbornane and the $P_9(5)$ skeleton analogous to noradamantane differ from the $P_7(3)$ cage only by the opening of one bond in the three-membered ring or by the substitution of the three-membered ring by a five-membered ring. The tetracyclic $P_9(3)$ skeleton can be obtained from the $P_7(3)$ skeleton by the condensation of a five-membered ring onto the latter structure with the aid of a two-atom bridge. Moreover, the $P_7(5)$, $P_8(6)$, and $P_9(5)$ skeletons are essential structural unit groups of Hittorf phosphorus[128]. It is these structural relationships that are responsible for the easy reciprocal transformations and the simultaneous genesis of the various species.

If the class of structurally ascertained molecular polycyclic phosphane derivatives is also taken to include the "inorganically" substituted $P_{11}(SiMe_3)_3$, which according to *von Schnering et al.*[129] contains a symmetric skeleton of six condensed five-membered rings, the outstanding significance of the formation of five-membered ring structural elements in polycyclic phosphane skeletons becomes clearly evident. This is an essential difference from carbon chemistry, and among other things it explains why it has not yet been possible to prepare a molecular decaphosphaadamantane[38, 130]. The mass-spectroscopically identified compounds $P_{10}R_6$ (R = *i*Pr[115], H[3d]) must have some other structure. In contrast to several three-membered and six-membered partial frameworks, structure elements made up of four-membered rings or from rings of more than six P-atoms have not so far been encountered in sterically unhindered polycyclic phosphanes.

Summarizing, according to our present state of knowledge the structures of polycyclic phosphanes and their sterically unhindered derivatives are determined by the following criteria:

1. In accordance with the empirical formula, fundamentally the same formally derivable polycyclic structures may exist as in hydrocarbons of analogous composition, each P-atom substituted by a monofunctional residue corresponding to a CH_2 group and each P-atom bound only to phosphorus corresponding to a CH group.

2. Of the constitutional isomers possible according to point 1 above, those with the maximum number of five-membered ring elements are formed.

3. If the stoichiometric composition requires other

structure elements in addition to five-membered rings, then additional three-membered and six-membered rings are incorporated in the phosphane structure, but not four- or seven-membered rings.

4. Phosphane skeletons with three-membered rings are generally more thermally stable than ones with six-membered rings.

5. The structures of higher-condensed phosphanes are derived from those of lower-condensed phosphanes with two fewer P-atoms, often by the condensation of a new five-membered ring onto the latter structure *via* a two-atom bridge with *trans* substituents.

6. Particularly phosphorus-rich structures are built up by the linking of large partial frameworks (P_7-, P_8-, P_9-, P_{11}-), either by an exocyclic P—P bond or *via* the zero bridge of a commonly formed bicyclo[3.3.0]octaphosphane partial structure.

7. Constitutional isomers may be produced if several skeletons of similar structure and hence comparable stabilities are possible for one and the same empirical formula.

8. Of the various possible configurational isomers, the one produced is always that with the maximum *trans* arrangement of the substituents. The formation of further isomers is determined by the steric interactions when the structure deviates from the "all-*trans*" arrangement.

Thus, whilst the formulas of the polycyclic phosphorus hydrides listed in Table 1 may at first sight show no rhyme or reason, the application of these structure principles makes them largely comprehensible.

8. Summary and Future Prospects

Research in the last 15 years has led to the realization that compounds with a skeleton of phosphorus chains and rings are not in any way "exotic" in the field of nonmetal chemistry. With modern preparative techniques such compounds can be handled with little or no problem and in their structures they show many similarities to the corresponding hydrocarbons. This must be attributed to the equal numbers of valence electrons in the $-CH_2-$ and $-\ddot{P}H-$, and in the $\geqslant CH$ and $\geqslant P:$ groups. Analogous framework structures can therefore be produced. Certain differences do exist, due mainly to the following special features of phosphorus:

1. $\ddot{P}-\ddot{P}$ bonds enter easily into four-center reactions owing to their free electron pairs. Disproportionations and ring-rearrangement reactions therefore take place under considerably milder conditions than in the case of hydrocarbons or of hydrogen-silicon compounds.

2. Phosphorus tends to form smaller bond angles than carbon, and this can lead to different stability sequences among the cyclic compounds of the two elements.

3. As a result of the trivalence of phosphorus, chiral centers occur appreciably more often in open-chain and ring-type phosphorus compounds than in the corresponding compounds of carbon.

The present review should make it clear that we just stand at the beginning of an era of new and highly promising developments in the field of chain-type and ring-type phosphorus compounds. If we consider the number of phosphorus hydrides and organophosphanes that have already been identified by mass spectroscopy but not yet been made on a preparative scale, and whose structures still have to be confirmed experimentally, the scope and diversity of work ahead of us in the near future becomes very evident. Further stimulating investigations will arise from the question whether one could carry out aimed isomerizations from which information could be derived about the relative stabilities of the individual constitutional isomers and about the mechanism of these reactions. Another particularly fascinating subject is the valence tautomerism in phosphorus compounds. Furthermore, the reactive potential of the phosphorus three-membered ring compounds could prove to be useful in various preparative contexts. Studies in the various areas mentioned are currently under way in our laboratories.

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Conformation and Biological Activity of Cyclic Peptides**

By Horst Kessler*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

Cyclic peptides containing biologically active hormone sequences are suitable models for studying conformation-activity relationships. In such models the usual flexibility of peptide chains is reduced by their cyclic arrangement. However, conformational analysis of such systems by experimental means is possible only if a single conformer predominates at equilibrium, and criteria for this are put forward. NMR spectroscopic methods, including many recent advances, are discussed in relation to their ability to contribute to peptide conformational analysis.

Apart from consideration of the hydrogen bond, we organic chemists have really paid little attention to linkages other than the purely covalent. I believe that it will be the duty of organic chemists in the furture to study the weak non-bonding interactions which are of enormous importance in the large natural macromolecules. Such studies will lead to a new blossoming of organic chemistry in the future. *Lord Alexander R. Todd*[1]

1. Introduction

The planned synthesis of a totally selective drug with no side effects is the ambition of every pharmacologist and drug chemist. Efforts towards realizing this goal of drug design have been many[2–6], and the search for relationships between structure and activity has been the principal subject of activity in many industrial and academic laboratories. At the same time, the search for refinement of present-day concepts of the structure of organic compounds is reflected in the work of chemists, biochemists, and pharmacologists alike. Initial efforts at finding a connection between structure and activity equated structure with constitution, but it soon became evident that configuration was at least of equal importance. As a result, special emphasis has been placed in recent years on stereospecificity in the synthesis of active substances. The importance of molecular conformation in both chemistry and biochemistry has been evident ever since the pioneering work of *Barton*[7]; yet only hesitant efforts have since been made to establish a link between conformation and activity[8].

Perhaps it is not difficult to see why. Conformers are generally not isolable as stable compounds and therefore cannot be tested separately for biological activity. The cyclic tetrapeptide [Sar^1]-Tentoxin appears to be the only molecule known so far[9b] whose two conformers have been separately examined—and here in fact they have been found to differ in activity. Generally it is difficult enough even to determine the most stable conformation in solution, and all the more to follow changes in conformation in biological media[10, 11]. The only way out of this problem appears to be to effect *conformational* changes by altering the *constitution* and/or *configuration* of an active substance, but it would then be highly difficult to distinguish between the separate effects on biological activity of the various changed parameters.

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2. Hormone—Receptor Interaction

An alternative way out of this dilemma could be the study of certain physiologically active peptides which have recently been the center of interest as hormones and neuropeptides[12][*].

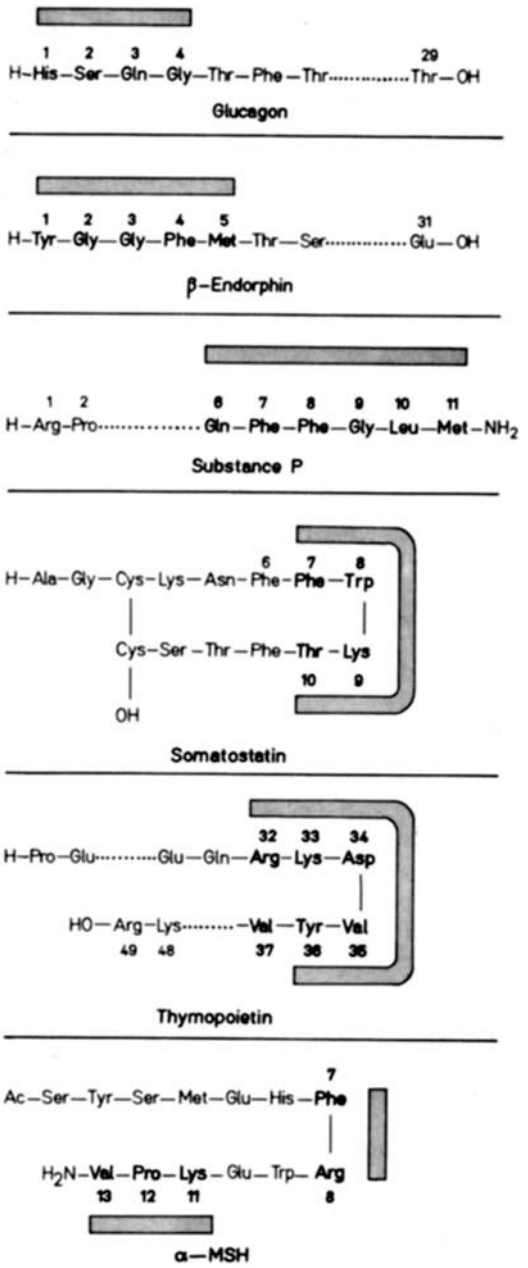

Fig. 1. Sequences of the active parts of peptides: glucagon [13, 14], β-endorphin [15], substance P [16, 17], somatostatin [18], thymopoietin [19], α-MSH [20].

In many of these compounds the "active region" is relatively small and comprises a sequence of only four to five amino acids (Fig. 1). Structural modifications in this region lead to particularly pronounced changes in biological activity. This should raise the question of whether the rest of the molecule merely serves to hold the active part in the "right" conformation. If so, changes in this "scaffolding" should lead to conformational changes which might be directly correlatable to changes in biological activity.

One possible way to put this idea into practice could be through models of hormone-receptor interaction. *Emil Fischer*'s "lock and key" principle, based on the binding[21] of the hormone to the receptor, and thus on "molecular recognition" is generally recognised as valid to this day. An encounter of this type is assumed to lead to conformational change in the receptor, which in turn causes "transduction" of a signal (Fig. 2). Complex formation and signal transduction are not necessarily interconnected. Hence, substrates which might complex with the receptor and yet fail to induce a signal (competitive inhibition) have been sought.

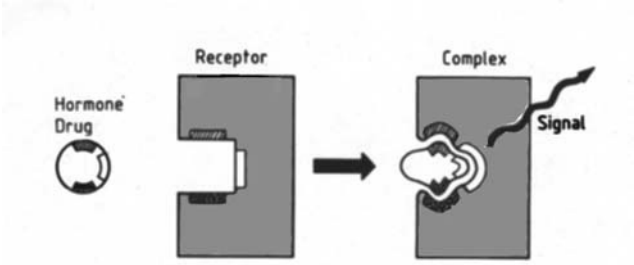

Fig. 2. Model of hormone- or drug-receptor interaction.

Complexation can also lead to conformational change in the hormone itself. In fact, the concept of "induced fit" is now thought to apply equally to the hormone and to the receptor (Fig. 3)[22]. It is immaterial for the purposes of the subsequent discussion whether a predetermined equilibrium or a change of conformation induced only during complexation is the more important factor. To begin with, it is appropriate to assume that the most stable conformation of the hormone in solution is the same as that in the complex with the receptor but that this may subsequently change. However, the structure of no invidual hormone receptor has been elucidated yet[23], and currently there are no methods to determine directly the relevant conformation of a hormone in association with the receptor. Hence, indirect methods must be sought.

One possible approach lies in determining the conformation of biologically active molecules by assuming that the more similar the conformation of the hormone in contact with the receptor is to its most stable conformation in

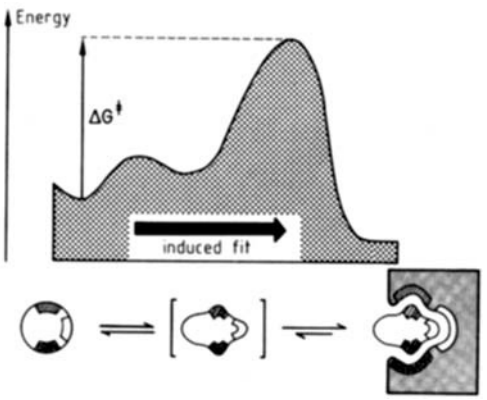

Fig. 3. Induced fit of conformations upon binding to the receptor.

[*] A matter of current interest is the synthesis of hormone agonists or antagonists (*e.g.* competitive inhibitors), which may lead to drugs for the treatment of hormonal disorders.

solution, the greater is the hormone's biological activity (Fig. 4). At the back of this is the argument that conformational change ensuing upon complexation would entail additional energy consumption at the expense of binding energy. There appears to be little force for this argument when it is considered that, in general, the energy change involved in changing conformation is of a much lower order of magnitude than the binding energies[*]. Nonetheless, the basic hypothesis of correlating the most stable conformation in solution with that at the receptor site does appear to justify the study of active molecules in solution; and it also seems safe to assume that at least some of the systems studied will indeed behave according to this hypothesis, in that conformational change upon complexation will not be unduly excessive.

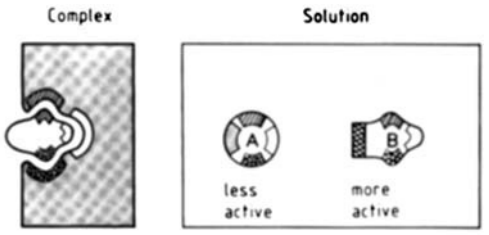

Fig. 4. Possibility I for determination of the conformation at the receptor. Hypothesis: The most active molecule already prefers a conformation in solution which is similar to the conformation in the complex.

Another possibility of obtaining information on the conformation at the receptor site is by introducing conformational restraint. This is illustrated schematically in Figure 5 by placing a "girdle" on the molecule. If the process of "girdling" leads to a geometry which does not suit the receptor, then no biological activity can be expected. If the girdling is in the right position then, on the other hand, activity should remain unchanged or even be enhanced. In practice, such modification of conformation can be achieved by cyclization, which restricts freedom of conformational movement, particularly in the case of smaller rings. In other words, this indicates that cyclic peptides should first be studied[25-27].

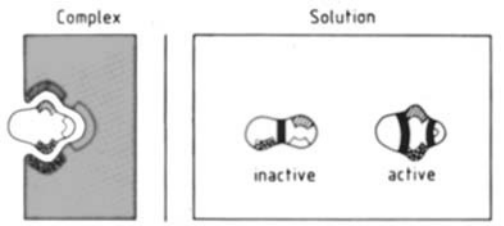

Fig. 5. Possibility II for determination of the conformation at the receptor by conformational restraint.

It seems appropriate to conduct such studies of conformational effects in the order indicated by the following headings:

[*] Typical binding energies of biologically active peptides are of the order of 12—17 kcal/mol [24], whereas energy changes of only fractions of a kcal/mol are sufficient to induce considerable conformational change.

1. Search for the active sequence in the hormone

This can be carried out using the classical procedure of varying the constitution and configuration of the amino acids in the peptide chain, until that part of the molecule has been located where minimal changes lead to maximal effect.

2. Conformational studies of biologically active molecules

First and foremost this involves studying conformational integrity under various conditions (*e.g.* in the crystalline state and dissolved in various solvents). In solution, in particular, the coexistence of several different conformations has to be taken into account; clear-cut results can, in general, be expected only in cases of proven conformational homogeneity. The less conformational transition occurs in solution, the more chance will there be that this will also be minimal on complexation with the receptor.

3. Conformational studies of model peptides

These, with variations in both constitution and configuration, should help to predict the conformations of analogous novel peptides.

4. Introduction of an active amino acid sequence into cyclic structures for simulation of conformation at the receptor site

On the basis of results with models, the non-active fragments have to be selected such that through their influence the molecule as a whole will be likely to assume the probable "active" conformation deduced from other studies on biologically active hormones. Thus, synthesis, conformational analysis, and biological activity measurements proceed hand in hand.

The study of *cyclic* peptides involves an important side aspect. In the organism, the breakdown of a peptide chain proceeds most easily starting at a C- or N-end group; hence the degradation of cyclic peptides is markedly slower, and their biological activity is more sustained[18,28-31]. Another aspect concerns reversed turns in cyclic structures. In linear peptides and proteins such loops are occasioned by the tendency to form intramolecular hydrogen bonds. Best known is the β-loop[32], which facilitates the antiparallel hairpin bending of peptide molecules and enables hydrogen bonding between C=O and NH groups of the first and fourth amino acids in a peptide sequence. In smaller acyclic or cyclic peptides the γ-loop, whose function is to facilitate analogous hydrogen bonding between the first and third amino acid in the sequence, is also encountered (see Fig. 17). The importance of these turns in the transmission of information can be rationalized thus:

It can be assumed in the following that the "lock and key" principle in nature will keep the transportable hormone "key" as small as possible, and that to ensure maximal information transfer this "key" will be sheathed three-dimensionally to the fullest possible extent. The receptor, on the other hand, can be relatively large in view of its fixed immobility (*e.g.* in the cell membrane). Such "sheathing" of the "region of encounter" would be most effective at chain terminals or helical loops which could efficiently penetrate inside a receptor pocket (cf. Fig. 1). It

thus seems reasonable to assume that active sequences locally concentrated within a peptide chain will indeed incorporate such looping. As for the rest of the molecule, its function would then be to ensure the proper conformation of the active region and the reinforcement of its connection with the receptor (see Section 2).

In this essay a short account of the experimental methods presently available for determining conformation will be presented. Here, NMR spectroscopy occupies a special place since this method is greatly superior to all others for supplying detailed information on conformation in solution[25-27,33-42]. The present discussion does not of course preclude supplementing our fount of knowledge by additional means, whether experimental[43-48] or theoretical, such as by molecular mechanical calculations[49].

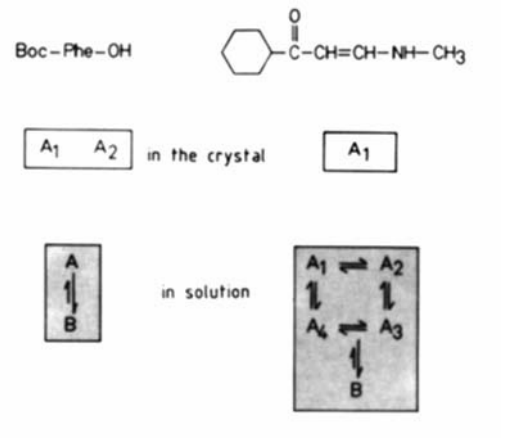

Fig. 6. Conformational changes upon dissolution of crystals (see text).

3. Conformation in the Crystal and in Solution

X-ray crystallography has now reached such a high state of development that, provided good crystals are available, structure determination of small molecules, in particular, has become a routine matter. No other method can rival it as regards accuracy and the advantages of direct pictorial representation. However, the information obtained is restricted to the crystalline state, and attempts frequently and thoughtlessly made to extend the validity of such information to the situation in solution are, on the whole, quite improper.

For those cases where the energy barrier between the most stable conformation in solution and that in the crystalline state is $>ca.$ 10—15 kcal/mol it is possible to follow the conformational change involved by dissolving the crystal at low temperature and following the change in the NMR spectrum after different time intervals and/or after raising the temperature[50-54]. This method frequently permits the assignment of discrete signals to particular conformations. In many other cases, however, energy barriers are so low that rapid conformational equilibria are established on dissolution. This problem can now be circumvented by the recently routinized CP-MAS (cross polarization magic angle spinning) technique[55], which yields high resolution ^{13}C-NMR spectra of solids and can thus provide a bridge to the results obtained from NMR spectroscopic studies of such substances in solution[55-60]. Undoubtedly this approach will also be of value in those cases where single crystals suitable for X-ray crystallography cannot be prepared. An example of the application of this method is the protected amino acid Boc-Phe-OH (*N-tert*-butoxycarbonyl phenylalanine) which exists in two discrete conformations in the crystal[54,59,61]. On dissolution, these equilibrate rapidly even at low temperatures and their separate NMR spectra cannot then be measured[54,62]. However, in solution there is a subsequent transition, with a relatively high energy barrier ($\Delta G^{\neq}_{298} = 16.0$ kcal/mol), to a third conformation which is more stable in solution than the other two[54,62] (Fig. 6).

In the vinylogous amide shown in Figure 6, there is only a single conformer in the crystalline state, and this rapidly undergoes equilibration on dissolution to give four other unstable conformations. After a little time these are almost completely transformed into yet another conformer, which is the most stable one[59]. A further interesting case is that of the cyclic tripeptide *cyclo*[Pro$_2$-NBGly] (NBGly = N(o-nitrobenzyl)glycyl)[63]. This crystallizes from CCl_4 and from MeOH in two different crystalline forms[64], and X-ray crystallography has shown that in both of these the ring has a boat conformation[53,65,66], in each case in a different spatial environment. However, in MeOH solution a crown conformation appears to predominate[63]. This at any rate was found by ^{1}H-NMR studies of first fractions obtained by crystallization from this solvent at low temperatures and redissolution at $-50°$, whereas crystals which had separated more slowly and were identical with those used for the above-mentioned X-ray work gave a spectrum indicative of a boat conformation[63].

The coexistence of several conformations appears to be the case in general in both solution and in the amorphous state. In the latter they are apparently "frozen"; in the high-resolution solid state ^{13}C-NMR spectrum broad signals, resulting from many conformers and from packing (molecular disorder) effects, are observed. In solution, on the other hand, rapid equilibration between numerous conformations must be assumed, and it is only when energy barriers separating these are between 5 and 25 kcal/mol that detailed information on the molecular processes involved in these conformational transitions can be expected from NMR spectroscopy[67-69]. Thus, generally speaking, conformational rigidity will be restricted to certain portions of the molecule, and conformational mobility will be inherent in other parts such as side chains. Even with molecules assumed to be relatively rigid, the question of conformational homogeneity is the one that has to be considered first. Frequently a "median" conformation has been proposed as a working hypothesis for flexible molecules, but as *Jardetzki* has clearly pointed out[70] this is physically meaningless in the majority of cases since there is no linear relationship between NMR data and geometrical parameters (see Section 4).

Before going into the means at our disposal for demonstrating conformational homogeneity it seems appropriate to discuss the type of information available in this field from NMR spectra.

4. NMR Spectroscopic Methods for Conformational Analysis of Peptides

The conformation of the peptide "backbone" can be expressed in terms of the angles ϕ, ψ, and ω, while the side chain can be characterized by the angles χ (Fig. 7)[71].

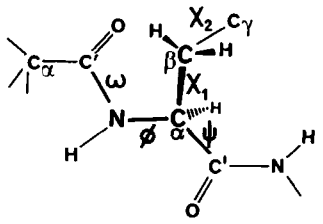

Fig. 7. Definition of the angles in peptides. The eclipsed orientation of the bonds along the peptide framework $-C_\alpha-C'-N-C_\alpha-$ corresponds in this sequence to a dihedral angle of 0°. The right-handed helical orientation is taken as positive.

The following parameters can be deduced from NMR spectra:

- Chemical shift δ
- Scalar coupling J (indirect through-bond coupling)
- Intensities
- Exchange broadening
- Dipolar through-space coupling evident by relaxation phenomena, *e.g.* spin-lattice relaxation times (T_1) and nuclear Overhauser effects (NOE).

After *extracting* these parameters from the spectra one has to *assign* them to molecular structures. *Interpretation* of the parameters, in turn, leads to the desired structural information (see Fig. 8). Although it seems obvious, it is just with relatively complex peptide structures that erroneous extraction and indiscriminate assignment of data have led to conclusions which turned out to be dubious, even though arrived at *via* critical interpretation. In fact, many previously reported literature data would seem to bear reexamination.

For the purpose of assigning signals to amino acids the search for coupling patterns[72,73] has been enormously simplified by the use of modern two-dimensional NMR techniques[74-76], such as homonuclear[73,77-79] and heteronuclear[76,80,81] 2 D-*J*-resolved spectroscopy[82], ^{1}H-^{13}C-2 D-shift correlation[76,80,81,83-85], and homonuclear 2D-shift correlated[11,78,80,81,83-85] spectroscopy. By means of NOE-difference spectra[85,88,89] or of 2D-NOE spectroscopy[90-94] it is now possible to sequence peptides without the need for tedious synthesis of selectively deuterated derivatives[97-99]. In cases where two conformers coexist in moderately rapid equilibrium, the exchange of individual nuclei between them can be demonstrated directly by saturation-transfer[53,65,99,100] or by 2D-exchange[94,101-106] spectroscopy.

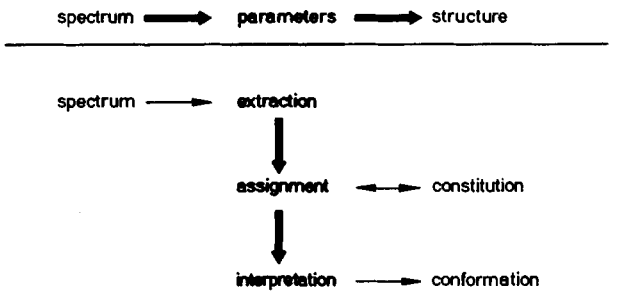

Fig. 8. Interpretation of NMR spectra.

Table 1 serves to summarize all currently available NMR techniques for determining peptide conformation.

Important first indications concerning molecular structure are provided by knowledge of the orientation of amide linkages, which on the whole is defined by hydrogen bonding (intra- or intermolecular or by interaction with the solvent). Intermolecular hydrogen bonds and those to the solvent are readily cleaved with increasing temperature, because the decrease in entropy, which goes hand in hand with solvent bonding, is increasingly evident at higher temperatures (Fig. 9). This is true for all hydrogen bonding solvents, and the most numerous and meaningful results have been obtained for solutions in DMSO[25,26,97,107-112]. In this solvent, generally speaking, temperature gradients for the chemical shift of the N*H*-signal in excess of 4×10^{-3} ppm/K are considered evidence of external NH-orientation, while values of under 2×10^{-3} ppm/K point to solvent shielding[*][97].

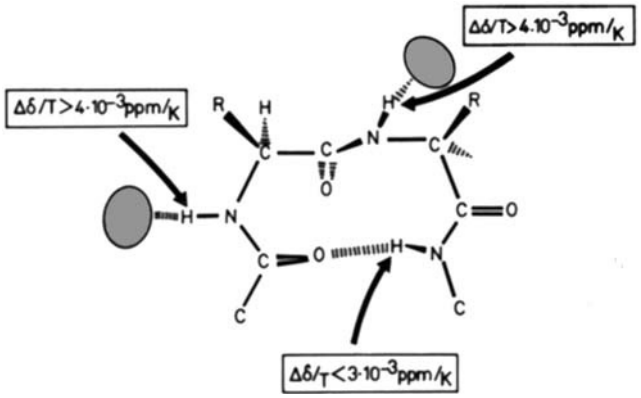

Fig. 9. Temperature gradients $\Delta\delta/T$ of the N*H* signals in dimethyl sulfoxide (DMSO) using the example of a β-loop.

Within the framework of conformational studies it is possible to interpret solvent effects only after ascertaining that a change of solvent does not induce a conformational change. Replacement of the strongly H-bonding solvent DMSO by $CDCl_3$ leads to a considerable shift to higher field of NMR signals of exposed N*H*-groups (Fig. 10)[113,114]. This effect is evident in mixtures containing more than 50% $CDCl_3$, because the interaction between this solvent and residual DMSO leaves insufficient of the latter to bond to the peptide[97]. Conversely, solvents which can act as H-donors for hydrogen bonding, such as trifluoroethanol (TFE), can shift the NMR signals of the neighboring N*H*-proton to lower field *via* "protonation" at

[*] Use of the δ-scale for chemical shifts necessarily leads to negative values for the temperature gradient defined by $\Delta\delta/T$. In the literature on the other hand, values are encountered which are positive for historical reasons (use of the τ-scale), and this review holds to the latter convention, *i.e.* a positive value indicates shift of the N*H*-signal to higher field with increasing temperature.

Table 1. Possible methods of determining the conformation of peptides by NMR spectroscopy.

Cause	Observed Spectral Parameter		Typical Information
Interaction with the environment	N*H*-shift as a function of: solvent, temperature		Orientation of the amide bond, H bonds
	Paramagnetically-induced spectral changes		Distinction between peripheral and inner nuclei
Interactions through-bonds	Scalar couplings:	vicinal coupling	Angles ϕ, ψ, χ
		geminal coupling of glycine H_α	Angle χ
		direct coupling ^{13}C-H	$C_\alpha CO$ angle
		direct coupling ^{15}N-H	*cis/trans*-Isomers of the amide bond
	^{15}N chemical shift		H bonds to neighboring CO
Interaction through space	Chemical shift:	^1H (anisotropic)	Orientation of aromatic side-chains
		^{13}C (steric and electronic effects)	*cis/trans*-Isomerization at proline
	Dipolar coupling:	NOE effect (^1H)	Intramolecular proton distances
Mobility	Line Coalescence		Processes with relatively high barriers
	Relaxation times ^{13}C (T_1 and NOE)		Mobility of side chains
Chemical exchange	H/D Exchange rates		Extent of exposure of the NH groups

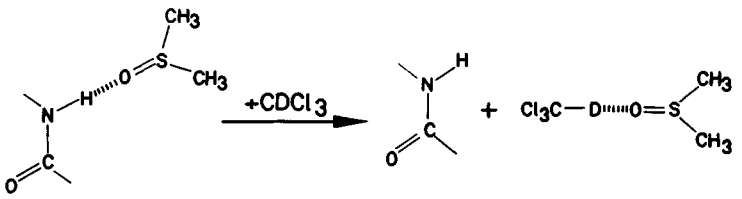

Fig. 10. Effect of titrating a DMSO solution of a peptide with $CDCl_3$. The removal of H bonds to the solvent at $CDCl_3$ levels of > 50% leads to a strong high-field shift of the N*H* signal.

the carbonyl oxygen (Fig. 11)[113, 114]; this effect however is more difficult to evaluate, since the addition of protic solvents also causes conformational changes.

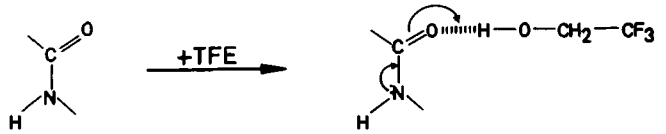

Fig. 11. Effect of adding a protic solvent (here: TFE) to a peptide. A shift of the N*H* signal to low field is observed because of "carbonyl protonation".

Vicinal coupling constants ^3J, whose dependence on dihedral angle is expressed by the Karplus equations, are of great importance in conformational analysis. As these functions are highly dependent on the type of substituent involved, special expressions derived empirically from a wealth of experimental data have been proposed for various different bond types[115–117]. Of particular importance is the easily measurable homonuclear $^3J_{HNC_\alpha H}$ type of coupling, which is dependent on the angle ϕ. However, it is difficult to achieve unambiguous results with such measurements, because of the ambiguity of the Karplus curve (most measured coupling constant can correspond to four different bond angles!) and the range of experimental error. The ambiguity problem can be solved in principle by evaluation of additional coupling constants for a particular bond (Fig. 12). This entails either special instrumental conditions, or the tedium of synthesizing peptides specifically enriched by ^{13}C and/or ^{15}N, since it is difficult to deduce heteroatom—proton coupling from a spectrum directly. For this reason there are only few instances where exhaustive treatment of multicoupling have been described[116, 117]. However, a recent development describing the use of two-dimensional NMR spectroscopy in dealing with heteronuclear coupling over more than one bond[118] should greatly improve the availability of such data.

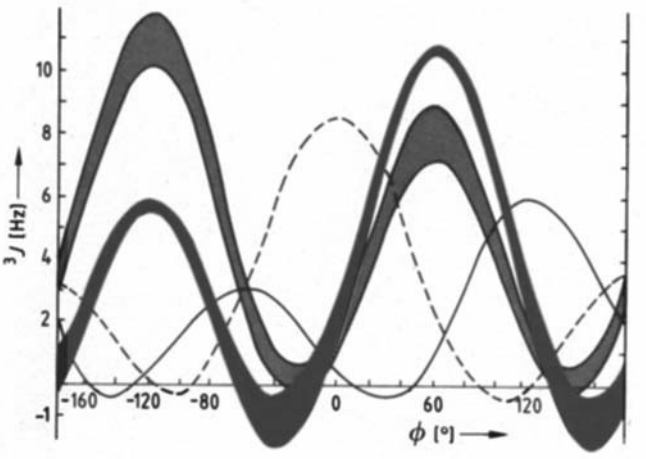

Fig. 12. Interpretation of the vicinal coupling constants for the determination of the ϕ angle (after *Bystrov et al.* [116]). ▨: $^3J(H—NC_\alpha—H)$; ■: $^3J(^{13}C'—NC_\alpha—^1H)$; —: $^3J(^1H—NC_\alpha—^{13}C_\beta)$; ---: $^3J(^1H—NC_\alpha—^{15}C')$. See Figure 7 for the definition of the angle ϕ (ϕ refers to the L-form).

The situation is different with conformations of side chains (angle χ). Here it almost always necessary to make the prior assumption of a rapid equilibration between several conformations which is analyzable by interpreting vicinal coupling constants (such as between the α-proton and the two diastereotopic β-protons within an amino acid residue)[115, 119, 120]. Proline is of special significance in this respect[27, 78, 121, 122] in view of its importance in the specific construction of peptide structures and the manner of folding of peptide chains in proteins[123, 124]. Here, on the one hand, the flexibility of the "side chain" is undoubtedly restricted by its attachment to a five-membered ring, but on the other, since this is a pyrrolidine ring, a rapidly established equilibrium between many conformations in such a system has to be taken into account. Originally, the discussion on the conformation of proline was based on the assumption of two rapidly equilibrating Ramachandran conformations[125], but later more exact analysis indicated that a greater range of pseudorotation must be taken into ac-

count[126-128]. Since, *e.g.* for the C_β—C_γ bond a total of four vicinal coupling constants (two *cis*- and two *trans*-couplings) is available for determining the angle, it is possible to arrive at a complete analysis of the equilibrium between several conformations by a series of iterative calculations[128, 129].

From the more easily available vicinal coupling data it is not generally possible to arrive at direct information on the angle ψ (N—C_α—C′—N), though in the case of glycine the value of ψ has been found to be related to the geminal coupling between the two α-protons[115, 130-132]. More recently, measurement of the direct ^{13}C-^1H coupling constant has been suggested as a means of determining the angles ψ and ϕ[133, 134].

A *trans*-conformation of the amide linkage ($\omega = 180°$) can now be deduced[85, 115] from the value for $^1J_{^{15}N-H}$, which has recently become more accessible by use of the INEPT technique[*][135, 136]. In linear and macrocyclic peptides such *trans*-peptide linkages (*Z*-conformations) have been observed in every case examined so far.

In a few instances it has been possible to use the long range coupling between α-protons in two neighboring amino acid residues[137] or between and α-proton and the δ-protons in a proline residue for sequence determination[78].

Chemical shifts *per se* are generally more difficult to exploit. One phenomenon which may possibly prove useful is that of the downfield shift of a ^{15}N-NMR signal encountered when the carbonyl group adjacent to the amino group participates in hydrogen bonding[85, 138-140]. Prior to this, information of this kind had not been available.

In using ^1H-NMR spectroscopic chemical shifts, anisotropy effects from neighboring carbonyl groups or aromatic side chains must be singled out first and foremost as a source of information on molecular geometry. Thus, the orientation of an α-proton of one amino acid residue in the plane of the carbonyl group of the adjacent amino acid leads to a considerable shift to lower field (Fig. 13, cf. [78, 85, 141, 142]). A characteristic example of the effect exerted by aromatic side chains is the upfield shift of the α-protons of lysine 9 by the neighboring indole ring of tryptophan 8 in the biologically active sequence of the peptide hormone somatostatin[143-146]. This effect of course prescribes a specific folding of the peptide chain and can therefore be used for diagnostic purposes with synthetic somatostatin analogues having potential biological activity[147].

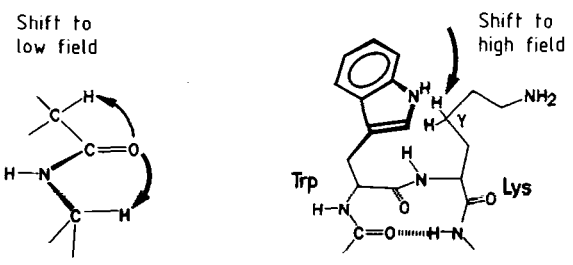

Fig. 13. Anisotropy effect on the chemical shifts of the γ-protons of lysine 9 of somatostatin due to the neighboring carbonyl groups and the aromatic side chain of tryptophan 8.

[*] INEPT = insensitive nuclei enhanced by polarization transfer.

As previously mentioned, amide linkages in peptides generally assume the *trans* (*Z*-) conformation. However, in peptides containing *N*-alkyl amino acid the presence of both conformations has to be reckoned with. The ^{13}C-chemical shift of C_β and C_α in proline rings, in particular, can give clear information on the stereochemistry at this bond[27, 37, 148] (Fig. 14).

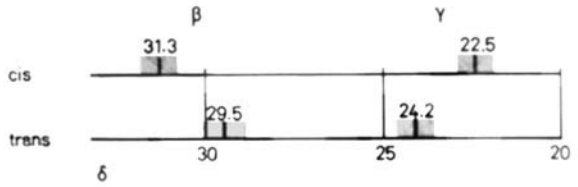

Fig. 14. Typical chemical shifts of the C_β- and C_γ-atoms for *cis*- and *trans*-Xxx-Pro-amide bonds in proline-containing peptides.

Siemion et al.[149] have put forward a quantitative relationship between the *difference* in chemical shifts between C_β and C_γ in proline and the angle ψ, and have also applied this to conformational analysis in a number of cases, but in our opinion their conclusions do not stand up to the test of critical examination[98].

Recently, the experimental determination of nuclear Overhauser effects (NOE)[150] has been facilitated by a number of improvements[88-94]. In one-dimensional NMR these effects manifest themselves by changes in signal intensity following irradiation at the resonance frequency of a nearby nucleus. Since homonuclear intramolecular NOE's between protons are caused by a dipolar relaxation mechanism there is a correlation between them and the distance between these protons. In most cases, however, NOE's can be observed only if that distance is not greater than 3—4 Å. In smaller molecules (in our case up to cyclic hexapeptides) NOE's are positive at medium field strength (*e.g.* when using a 270 MHz spectrometer) and under normal conditions (room temperature, DMSO as solvent). In proteins and at higher field strengths they are negative. In the latter case, the problem of spin diffusion[151-152] may arise, so that time dependence of NOE build-up is an additional factor to be considered[91, 153-155]. For further details the reader is referred to the literature cited.

NMR spectroscopy can also provide information on molecular dynamics phenomena. With exchange phenomena, *e.g.* the transition between several conformations or the exchange of NH-protons with the solvent, line broadening and signal coalescence are encountered when the energy barriers involved are in the range 5—25 kcal/mol[67-69]. Such conformational equilibria occur mainly because of rotation around the amide bond in peptides containing proline units[156] (rotational barrier *ca.* 20 kcal/mol), and in smaller cyclic peptides[50-53, 65, 66, 141, 142, 157, 158] where the ring reduces conformational freedom of movement. More rapid processes, such as the mobility of side chains in larger peptide molecules, can be followed by measuring ^{13}C spin lattice relaxation times (T_1) in cases where a dipolar relaxation mechanism is confirmed by the simultaneous measurement of a heteronuclear NOE[37, 41, 159, 160].

Only limited conclusions can generally be drawn on thermodynamic stability by following the course of a

chemical reaction, and this also applies to the information obtained in some instances on the "exposure" of NH-groups within a conformation by following the rate of exchange with deuterons (from added D_2O)[161, 162] or by saturating the H_2O signal and following the saturation transfer[99, 163] to the NH-signal[164–166]. In all likelihood, 2D-exchange spectroscopy will in future be used more frequently for studies of this kind[167]. In situations where any one conformation is strongly favored in a cyclic peptide, one would expect that NH protons directed outwards would be exchanged much more rapidly than those directed inwards, which are also more likely to participate in intramolecular hydrogen bonding. Admittedly, such arguments would fail in cases of rapid equilibration with another conformation (albeit less populated), where perhaps an even faster exchange of such "inner" NH protons might occur. This is merely one example to illustrate that in this approach to interpreting exchange rates one has to proceed with caution.

We have seen that NMR spectroscopy is a most versatile method for obtaining information on peptide conformation in solution. Of course, this review cannot cover the various techniques employed in more detail, but it does aim to provide a guide for the reader to the various options open to him.

5. Conformational Homogeneity in Solution

In Section 3 it was stressed that it must first be ascertained whether one is dealing with conformational homogeneity in tackling the problem of peptide conformation in solution. The reason why this principle was violated in this survey by treating this subject in Section 4 is because a familiarity with the NMR techniques in conformational analysis is desirable before detailed questions of conformational homogeneity are dealt with. Whereas as previously mentioned rapidly established equilibration between various conformations has to be considered as the norm for peptides in solution, it can also be assumed that the mobility can differ greatly in different parts of the peptide molecule. Thus, in smaller cyclic peptides we can expect greater rigidity from the peptide framework "backbone", and greater relative mobility for the side chains.

Strictly speaking, everything mentioned in Section 4 about using NMR spectroscopic techniques is valid only when the molecule assumes a single conformation, or where one conformation is so dominant at equilibrium that the effect of others on spectroscopic parameters is negligible. Statements on so-called "median" or "average" conformations should be treated with the greatest caution[70]. The problem is that all evidence on conformational homogeneity is indirect in nature. It is only the sum total of many different items of evidence which ensure a reasonable extent of certainty on this point.

In general, differences in chemical shifts, coupling constants, and temperature dependence between different amino acids in the peptide sequence can be used as indicators of conformational homogeneity; the smaller these differences, the greater the likelihood that a rapidly established conformational equilibrium will cause an averaging-out of these parameters. An example is provided by the cyclic pentapeptides. These are of special interest because they are the smallest cyclic peptides in which all amide linkages can have an unstrained *trans*-conformation, and in which we can expect a relatively strong inhibition of mobility. *cyclo*[Gly_5] and *cyclo*[Phe_5] show only a single set of glycine and phenylalanine signals, respectively, in the ^1H- and ^{13}C-NMR spectrum[97, 168]. The explanation could either be an inherent C_5-symmetry of the molecule, or a five-fold degenerate, rapidly established equilibrium of one or more conformation types[*] (median C_5-symmetry)[170, 171]. Evidence for the latter assumption is provided by the average temperature gradients for the NH-signal chemical shifts: $\Delta\delta/T = 2.96 \times 10^{-3}$ ppm/K (Gly), and 3.71×10^{-3} ppm/K (Phe). Introduction of a "symmetry distortion" in such compounds, *e.g.* by replacing the *pro-S* proton of the glycine unit by a methyl group (*i.e.* forming *cyclo*[Ala-Gly_4])[98] leads to pronounced differences in NH-shift temperature gradients for the separate amino acids units (see Fig. 15). Here, the methyl group appears to occupy a preferred position (thermodynamically) within its conformation(s). In *cyclo*[Phe-Gly_4], which has an even larger side

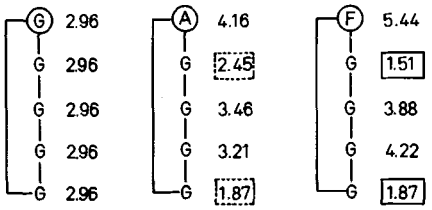

Fig. 15. Temperature gradients of the N*H* signals of three cyclic pentapeptides of type *cyclo*[Xxx-Gly_4] in DMSO [10^{-3} ppm/K] (see text); G = Gly, A = Ala, F = Phe (international single-letter symbols).

chain (benzyl groups)[97, 98, 168], the differentiation in the NH-shift temperature gradients is even more pronounced, as are those of the chemical shifts and coupling constants of the two diastereotopic α-protons in the glycine units[168]. Here, we can conclude that one conformation is predominant at equilibrium. After assignment of signals had been performed by synthesizing specifically deuterated deriva-

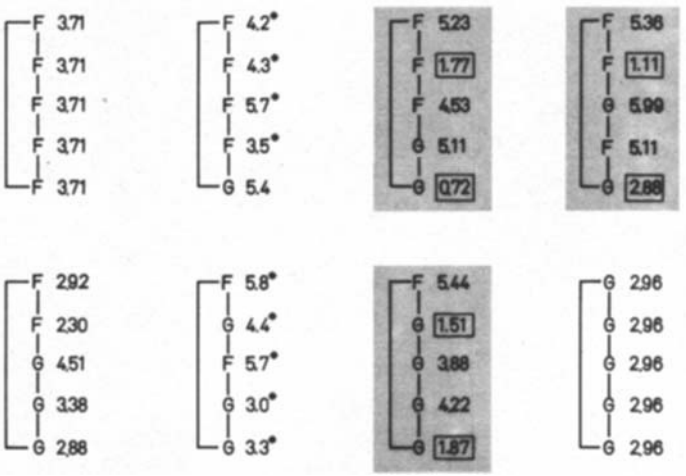

Fig. 16. Temperature gradients of the N*H* signals of all the cyclic pentapeptides of L-Phe(F) and Gly (G) in DMSO [10^{-3} ppm/K]. The three peptides on the shaded background are probably conformationally homogeneous. The values with asterisk were not assigned sequentially.

[*] In [168] it has been demonstrated that, *e.g.*, the transformations: $\beta_1\gamma_2 \rightleftharpoons \gamma_1\gamma_2 \rightleftharpoons \gamma_1\beta_2$ *etc.* occur easily and involve no great barrier.

tives, it was concluded[98] that an γ,γ-conformation (cf. Fig. 17)[109,111] is the most probable. Similar evidence of possible conformational homogeneity has been found in three of the eight possible pentapeptides containing only L-phenylalanine and glycine units (Fig. 16). The remaining five are thus to be considered as conformational mixtures and are unsuitable for conformational studies.

Altogether *ca.* 20 cyclic pentapeptides have so far been found likely to be conformationally homogeneous[85,97,109-111,172-180]. In these molecules two basic types can be distinguished, each with two intramolecular hydrogen bonds: the β,γ- and the γ,γ-conformation shown in Figure 17. The main aim of these studies was to find out

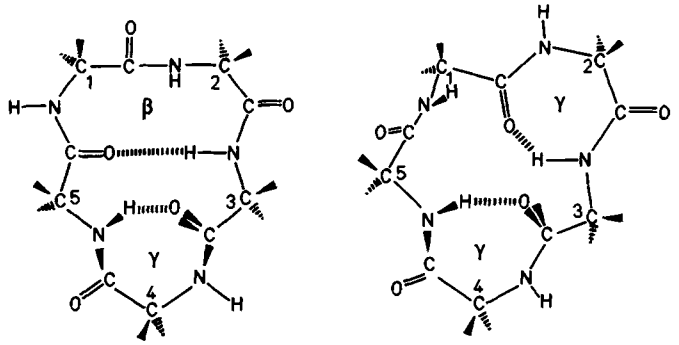

Fig. 17. The two most important conformations of cyclic peptides.

whether specific amino acid units tend to occupy specific sites within a given conformation. The results obtained so far can be summarized as follows[109,111]:

- Position 3 (Fig. 17) is usually occupied by glycine or a D-amino acid
- Position 4 in the γ-loop is generally taken up by a sterically demanding unit (Pro, Val, Phe, Aib)
- Proline preferentially occupies position 1 or 4

These and other results should make it possible to predict the most stable conformation of a peptide with a given amino acid sequence, or alternatively to forecast the best sequence to fit a desirable conformation. These results also show that for predominance of any particular peptide conformation, the exact nature of a side chain is of less importance than the absolute configuration. Thus, the four cyclic peptides shown in Figure 18, which have in common a sequence of three L-amino acids and two glycine units, have the same conformation in DMSO solution, whereas replacing L-Phe in position 2 in the cyclic peptide *cyclo*[Phe_3-Gly_2] by D-Phe leads to a marked change in the NMR parameters. In Figure 18 the N*H*-shift temperature gradients are used as the principle criteria[98,111], but other NMR parameters behave similarly.

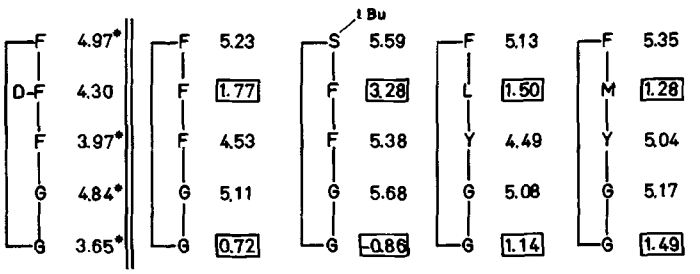

Fig. 18. Temperature gradients of the N*H* signals of some cyclic pentapeptides in DMSO [10^{-3} ppm/K]. The two first peptides from the right are cyclic enkephalins. F = L-Phe, D-F = D-Phe, G = Gly, L = Leu, M = Met, S-tBut = Ser(O-*t*Bu), Y = Tyr.

Of course, the minimal extent of side-chain influence on preferred peptide conformation is not encountered in every case. For example, replacing phenylalanine by serine in the i + 2-position of a β-loop is found to enhance the instability of that loop[110,181], and serine, in particular, is known to cause breakdown of β-structures[182,183].

The main indicators for conformational homogeneity are summarized as follows:

- Strong differentiation of temperature gradients of the N*H*-signals between separate amino acid units
- Similarly strong differentiation between chemical shifts of like amino acid units within the sequence
- Large chemical shift differences between geminal diastereotopic glycine protons
- Strong differentiation between vicinal coupling constants of diastereotopic protons (N*H* to both α-protons in glycine, and $C_\alpha H$ to both diastereotopic β-protons in other amino acid units)
- Large differences between N*H* $C_\alpha H$ coupling constants (a value of *ca.* 7.5 Hz can be interpreted as the mean for free mobility).

In additions to the absence of the above, the following can be taken as indicative of conformational heterogeneity:

- Non-linearity of N*H*-shift temperature gradients
- Change in coupling constants following change of solvent.

6. Conformation of Cyclic Peptides with Biologically Active Amino Acid Sequences

The need to restrict the mobility of peptide molecules in order to obtain information on their conformation has been discussed on a number of occasions[27-31,97]. So far, structure-activity relationships have been studied mainly on the basis of changes in constitution. Noteworthy contributions, which also take conformation into account, are *e.g.* those of *Hruby et al.* in connection with oxytocin[21], and above all those of *Veber*'s group on somatostatin[28-30,190]. The various steps leading to the development of the biologically highly active minisomatostatin are exemplary in illustrating this kind of study and are therefore summarized here.

Somatostatin[184], a tetradecapeptide containing a disulfide bridge between Cys-3 and Cys-14 (see Fig. 1) is formed in the hypothalamus and other endocrine glands (*e.g.* pancreas D-cells)[185,186]. It acts by inhibiting the release of peptide hormones such as glucagon, insulin, gastrin, secretin, and the growth hormone[185,186]. Activity studies on derivatives had previously shown that amino acids Ala-1 and Gly-2, which are not part of the ring, could be omitted without loss of activity, and that replacing tryptophan 8 by its enantiomer (D-Trp) resulted in an eightfold

increase in activity[187-189]. Together with numerous NMR studies on somatostatin[*] itself, these results were explained[143-146] by assuming that the sequence Phe^7-Trp^8-Ly^9-Trp^{10} is part of a β-loop. *Veber*'s group then synthesized somatostatin derivatives in which ethylene replaced the disulfide bridge[28,29,31], as well as bicyclic analogs with decreasing ring size[29,30]. These studies have ultimately led to the highly active cyclic hexapeptide "minisomatostatin"[147,190,191] in which only the sequence 7—10 of the original hormone is retained and the rest has been replaced by phenylalanine and proline. In this work NMR results on bicyclic intermediates and computer calculations on bridging in the conservation of a biologically active conformation were of paramount importance in setting the right course. Above all, the combination of instrumental and computational work made it possible to effect a drastic reduction in the number of derivatives which had to be synthesized and tested biologically.

Similarly, cyclic derivatives of enkephalins[111,192-200] and other cyclic peptides containing any biologically active sequences will also help to clarify the relationship between conformation and activity.

7. Conclusion and Outlook

NMR spectroscopy is an excellent probe for recognizing molecular conformation, because it responds to individual atoms in their specific environment. Since it can be used favorably to study molecules in solution, it fulfills the requirements for the investigation of intra- and intermolecular interactions. In addition it also provides considerable information on molecular dynamics.

Considerable advances in resolution and sensitivity in NMR spectroscopy have been brought about by the use of superconducting magnets and the discovery of 2D-NMR techniques. However, they also had a significant effect on the rapid, ever continuing development of NMR techniques to solve more and more complicated problems. Even the spectra of complicated natural products can now be reliably analyzed and assigned.

Apart from their roles in the transport of energy and material, natural products have an important function in information transfer. This involves weak interactions with the environment (*e.g.* hormone-receptor interaction, enzyme-substrate interaction, intercalation in nucleic acids, incorporation into membranes).

Individual weak interactions, because of their small magnitude, are difficult to detect *energetically*; however, they find their *geometrical* expression in conformational changes in the molecules involved. The order in the crystalline state, which can be represented by X-ray structure analysis, is contrasted in solution by considerable conformational multiplicity. The conformation can be changed by the influence of the solvent, by complex formation with metal ions, or by a biological receptor. Even these changes can be followed by NMR spectroscopy by incorporating molecules into membranes. Studies of this type, which I consider to be a prerequisite for "conformative drug design" will be of the greatest significance in the future.

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[*] The NMR studies, however, also indicated that somatostatin is still highly flexible in solution [143, 146].

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(Oxamidoximato)(oxamidoxime)platinum(II) 7,7,8,8-Tetracyanoquinodimethanide: A Crystal Structure with Segregated Parallel Stacks**

By *Helmut Endres**

The organic acceptor 7,7,8,8-tetracyanoquinodimethane ("tcnq", 2,2'-(2,5-cyclohexadiene-1,4-diylidene)bispropanedinitrile) is known as a component of "organic metals", which contain segregated parallel stacks of tcnq and planar organic donor molecules[1]. Attempts to obtain compounds crystallizing in this type, in which one of the two organic components is replaced by a planar metal complex, have been unsuccessful until now. Only the crystal structures of a few bis(arene)metal-tcnq salts with segregated stacks of the two components are known[2]. Such a structural type with a planar transition metal complex should be favored by hydrogen bonds between the two components. Bis(oxamidoximato)platinum(II) appears to be a suitable metal complex, since the α,β-dionedioximato complexes of the Ni triad crystallize in stacked structures[4] and oxamidoxime ("diaminoglyoxime", $oaoH_2$) with its amino groups readily forms H bonds.

The blue-black title compound was prepared by mixing methanolic solutions of Li(tcnq) and $Pt(oaoH_2)_2Cl_2$. The X-ray crystal structure analysis[11] (Fig. 3) indicates that the salt crystallizes in the desired structural type. Since the compound is paramagnetic, and is not obtained when neutral tcnq instead of Li(tncq) is used, it is assumed that tcnq is present in monoanionic form. This is also in accord with the CN stretching frequency, which is observed as a doublet at 2165 and 2200 cm^{-1} (cf. Li(tcnq): 2180 and 2210 cm^{-1}, tcnq: 2225 cm^{-1}). The metal complex must be a monocation, since the ratio metal complex: tcnq = 1 : 1; hence, only one of the two oxime ligands has lost a proton. Although the positions of the H atoms could not be determined, the structural analysis gives a clue about the position of the "surplus" H atom: the intermolecular O-O distance (255 pm) between the oxime oxygen atoms of the neighboring metal complexes in the *y*-direction indicates an intermolecular H bond between these; in addition, the usual intramolecular H bonds in bis(dioximato) complexes occur. The "additional" proton, therefore, links neighboring metal complexes; this has also been observed *e.g.* in the complex $Ni(oaoH)_2 \cdot HCl \cdot H_2O$, in which the position of this H atom could be determined.

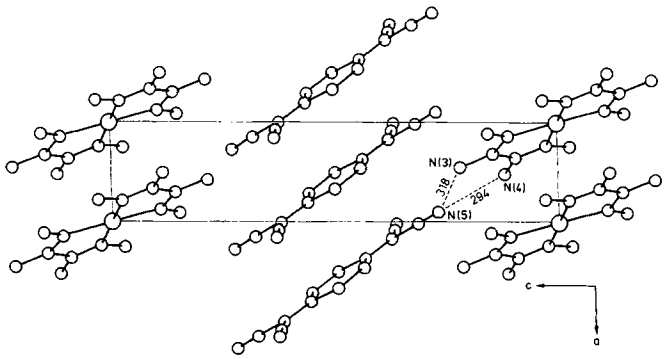

Fig. 3. Projection of the structure of the title compound in the *ac*-plane. Some of the H bonds between the metal complex and tcnq are indicated. Pt is located at the origin of the centric unit cell, and the midpoint of tcnq at the inversion center at 1/2, 1/2, 1/2.

Cations and anions form regular parallel stacks in the *x*-direction; the interplanar distances are 341 pm in the metal complex and 320 pm in the $tcnq^{\ominus}$ stack. This structure, in which every tcnq molecule carries a complete negative charge, leads one to expect semiconductor behavior for the compound[10]. Consistent with this is the fact that the conductivity of the compound is approximately a factor of 50 higher than that of Li(tcnq). Thus we have synthesized the first compound with segregated parallel stacks of a planar metal complex and tcnq, and have characterized it by X-ray structure analysis.

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[10] J. B. Torrance in [1], p. 7; *Acc. Chem. Res. 12* (1979) 79.
[11] Triclinic, $P\bar{1}$, $a = 379.7(3)$, $b = 755.0(5)$, $c = 1737.1(10)$ pm, $\alpha = 89.24(5)$, $\beta = 92.44(5)$, $\gamma = 94.42(4)°$, $V = 496 \times 10^6$ pm^3, $Z = 1$, $\rho_c = 2.12$ g cm^{-3}, $R_w(R) = 0.065$ (0.078) for 2152 reflections.

Reaction of α-Cyanophenylacetaldehyde with Sulfonyl Chloride

By *Ulrich Hertenstein**

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

α-Cyanophenylacetaldehyde **1** reacts[1] with sulfonyl chloride in CCl_4 to afford the novel 3-chloro-2-cyano-2-phenyloxirane **2** (85%)[2a]. In contrast, in benzene the reaction proceeds to give α-cyano-α-chlorophenylacetaldehyde **3** (88%)[2b]; both **2** and **3** are strong lacrymatory agents and allergens. **2** is cleaved by secondary amines such as

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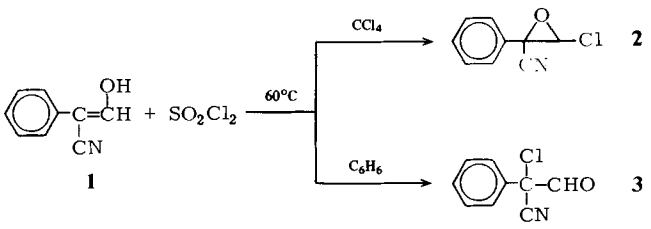
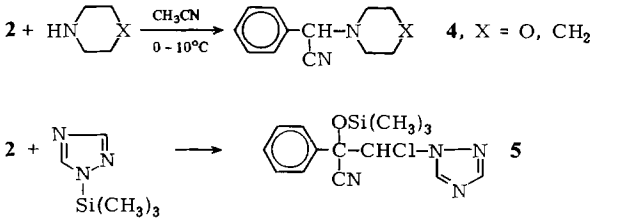


morpholine or piperidine to yield cyanides **4**[3] (yields 74% and 68%, respectively).



The adduct **5** (71%)[4] is obtained with trimethylsilyl-1,2,4-triazole.

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[1] **1** is suspended in the solvent at 60 °C and treated with sulfonyl chloride. The solution is held at 60 °C until no further evolution of gas is observed, is then degassed for 15 min with nitrogen, concentrated using a rotary evaporator, and distilled.

[2] a) **2**: B.p. = 115–116 °C/10 torr; ^{1}H-NMR ($CDCl_3$): δ = 5.9 (s, 1H), 7.5 (s, 5H); IR: no absorption between 2000 and 1610 cm^{-1}; b) **3**: B.p. = 91–93 °C/0.3 torr; IR: $\nu_{C=O}$ = 1740 cm^{-1}.

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[4] The equivalent amount of trimethylsilyl-1,2,4-triazole is added to pure **2** under conditions of moisture exclusion and ice cooling. After 20 min the mixture is distilled, b.p. = 132–134 °C/0.005 torr; m.p. = 98 °C; ^{1}H-NMR ($CDCl_3$): δ = 0.25 (s, 9H), 5.55 (s, 1H), 7.45 (m, 5H), 8.05 (s, 1H), 8.20 (s, 1H).

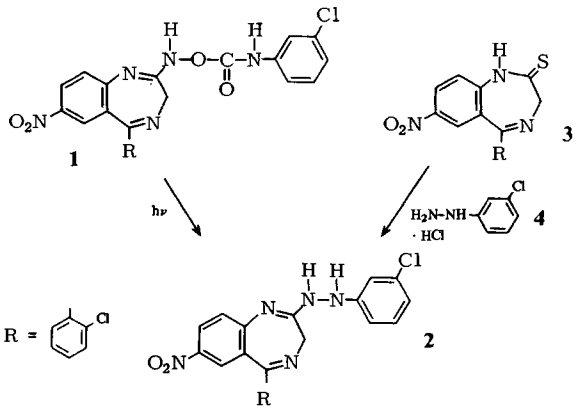
Light-Induced Decarboxylation of Carbamoyloxyamino Compounds

By *Gregory M. Shutske* and *Manfred Försch**

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

In the search for novel anxiolytic compounds we found carbamoyloxyamino-1,4-benzodiazepines with an interesting profile[1], but which, in part, slowly decompose in light. Hence, *e.g.* a pale orange coloration, which increases with the exposure time, is observed when the solid nitro derivative **1** is exposed to sunlight. A novel compound was detected in the thin layer chromatogram of the mixture. The MS (*m/z* 239 (M^+)) allows a light-induced cleavage of CO_2 to be assumed. Proof that the decomposition product is **2** was provided by synthesizing it from the known thione **3**[2] and 3-chlorophenylhydrazinium chloride **4**.

Until now, light-induced decarboxylations of carbamoyloxyamino compounds were unknown. The thermal decarboxylation of *in situ* formed 2-ethoxycarbonyloxyamino-1,4-benzodiazepines to 2-amino-3-ethoxy-1,4-benzodiazepines has recently been described[3].



Procedure

2: A solution of **3**[2] (3.3 g, 10 mmol) in 20 mL of dimethylformamide at 50 °C is treated with **4** (1.8 g, 10 mmol) and $NaHCO_3$ (2.0 g, 24 mmol). After being stirred for 1 h at 50 °C and subsequent TLC control, the oil is extracted with CH_2Cl_2/water; the organic phase is separated off, dried, and concentrated *in vacuo* using a rotary evaporator. After purification by column chromatography (silica gel; CH_2Cl_2/EtOH (9 : 1), orange needles of analytically pure **2** (0.6 g) are obtained (decomp. = 159–160 °C, isopropyl alcohol)[4].

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[4] R_f = 0.69 (CH_2Cl_2/EtOH (9 : 1)); ^{1}H-NMR ([D$_6$]DMSO): δ = 4.5 (s, 2H), 6.6–8.4 (m, 11H), 8.9 (s, NH), 9.7 (s, NH); IR (KBr): 1575, 1595, 1615 cm^{-1}; UV (CH_3OH): λ_{max} = 275 nm (lgε = 4.30), 373 (3.98).

ThI_3, A Janus amongst Compounds with Metal-Metal Interactions**

By *Horst P. Beck** and *Cornelia Strobel*

In the thorium-iodine system, ThI_2[1a] and ThI_4[1b] have been unambiguously characterized and their structures are known. Until now, the only indication that ThI_3 exists was based on thermoanalytical studies of the phase diagram[2]. X-ray powder diagrams of samples of this composition could not be interpreted[2]. We now report the preparation and single crystal structure determination of ThI_3.

Starting from ThI_4, which was synthesized directly by reaction of the elements in Duran ampules at 350 °C and multiple sublimation *in vacuo*, we obtained samples of ThI_3 *via* a symproportionation reaction with Th metal at 680 °C in sealed tantalum ampules. Two different forms of the product are obtained in this reaction: After short reaction times (2–3 d) thin, shiny-black, cylindrical rods were observed ["α-ThI_3", space group B2/b or Bb with pseudoorthorhombic metrics (a = 787.0, b = 2699.1, c = 3149.2

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pm, $\gamma \approx 90°$); at low diffraction angles X-ray diffraction gave a pseudohexagonal reflection pattern]. After longer tempering (4—6 weeks) compact, dark crystals having a slight green to brass colored luster on smooth surfaces were formed ["β-ThI_3, for crystal data[3] see Table 1]. This

Table 1. Crystal data of ThI_3 ("β-modification"), space group Cccm, $a = 873.5(2)$, $b = 2029.7(6)$, $c = 1466.1(3)$ pm, $Z = 16$, $\rho_{calc} = 6.26$ g/cm^3.

Atom	Th(1)	Th(2)	Th(3)	I(1)	I(2)	I(3)	I(4)
Point site	4 d	4b	8l	8k	16m	16m	8l
x	0	0	0.3270(3)	1/4	0.2894(4)	0.1133(4)	−0.0318(6)
y	1/2	1/2	0.1716(1)	1/4	0.4510(2)	0.3773(2)	0.1994(2)
z	0	1/4	0	0.1826(3)	0.1302(2)	0.3708(2)	0
B (Å^2)	3.09	3.15	3.17	4.33	3.54	3.87	4.09

modification of ThI_3 is an interesting variation of the "one-dimensional metals", which should be compared[5] with the structures derived from the TiI_3 type[4]. Th(1) has a cubic and Th(2) and Th(3) have a square-antiprismatic coordination of I atoms in β-ThI_3. The average Th—I distances are 330, 322, and 325 pm, respectively, and are very similar to those in ThI_4 (313—329 pm) and in ThI_2 (320—322 pm). The formulations $Th^{4+}(2e^-)I_2$ and $Th^{4+}(e^-)I_3$ indicate that the valence electrons are delocalized in a quasi-metal bond or are engaged in Th—Th interactions. The first of these possibilities applies to ThI_2 in which metallic conductivity was detected. In contrast, in ThI_3 both principles are combined. In Figure 1, only the framework of the

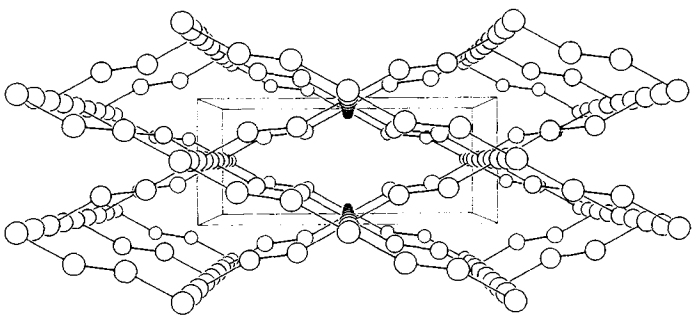

Fig. 1. Framework of the Th atoms in ThI_3 ("β-modification"). Viewed along [001].

metal atoms is shown. A strictly equidistant (366.5 pm) linear arrangement of Th atoms with alternating cubic and square-prismatic coordination by I atoms is found parallel to [001]. At the site of the cubically coordinated metal atoms, the strands are crosslinked by slightly wavy Th chains as "cross-connections" parallel to [110] and [1$\bar{1}$0]. In these chains, longer (380.0 pm) and extremely short (346.0 pm) Th—Th distances alternate. The distances in the Th_2 dumbells are *ca.* 4% shorter than in Th metal (360 pm): the distance between the dumbell atoms and the atoms in the linear chain is only around 5.5% longer, and is still shorter than the Th—Th distances in the metallic conducting ThI_2 (397 pm). The alternatives—equidistant *versus* dumbell-shaped atomic arrangement—are also known in other compounds with metal-metal interactions in chains. Often a transition from delocalization to localization of the valence electrons occurs at a critical temperature. This β-modification of ThI_3 is a "Janus" amongst compounds of this type, since one part of the metal framework appears to be in a state above and the other part, in contrast, in a state below such a critical temperature.

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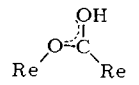
A μ_3-CO_2 Bridged, Tetranuclear Carbonylrhenium Complex: $[(OC)_5Re(CO_2)Re(CO)_4]_2$**

By *Wolfgang Beck**, *Klaus Raab*, *Ulrich Nagel*, and *Manfred Steimann*

Pentacarbonyl(tetrafluoroborato)rhenium is a particularly reactive starting compound for reactions with σ- and π-donors[1]. Reaction of $(OC)_5ReFBF_3$ with aqueous alkali (20 °C, molar ratio $(OC)_5ReFBF_3/NaOH \approx 1$) results in the precipitation of a colorless product of analytical composition "$Re(CO)_5OH$" **1** (yield 95%), which slowly turns pale jellow in light; the reaction—as determined by potentiometric titration—involves the consumption of one equivalent of OH^- per Re. From its IR spectrum (νCO_2: 1458 s, 1180 s, 1165 sh cm^{-1} in KBr; deuteration only shifts these bands by a maximum of *ca.* 5 cm^{-1}) **1** contains the structural element



The carboxy group in **1** is formed *via* the well known "base reaction"[2] of the metal carbonyl *i.e.* by nucleophilic attack of hydroxide ion at one of the carbon monoxide ligands. Thermolysis (100—150 °C) of **1** affords $[Re(CO)_3OH]_4$[3] and CO; rapid heating to above 200 °C gives CO_2 as detected in the mass spectrum. The action of hydrochloric acid on **1** affords, practically quantitatively, $(OC)_5ReCl$.

The crystalline, colorless, air-stable compound **2** (yield 56%) was obtained from the solution of **1** in acetone (20 °C). IR: 2148 m, 2088 m, 2039 vs, 1992 sh, 1983 s, 1965 sh, 1936 s, 1891 w cm^{-1} (νCO) in THF; 1380 s, 1295 m, 1260 w cm^{-1} (νCO_2) in KBr. In the mass spectrum (140 °C) of **2** the highest mass fragment found was $[Re_2(CO)_{10}O]^+$ ($= [(OC)_4Re(CO_2)Re(CO)_5]^+$). X-ray structural analysis of **2** shows a tetranuclear framework with CO_2 bridges, with every atom of the two CO_2 ligands being bonded to a rhenium atom having a noble gas configuration (Fig. 1).

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[**] Organometallic Lewis Acids, Part 10.—Part 9: B. Olgemöller, H. Bauer, H. Löbermann, U. Nagel, W. Beck, *Chem. Ber. 115* (1982) 2271.

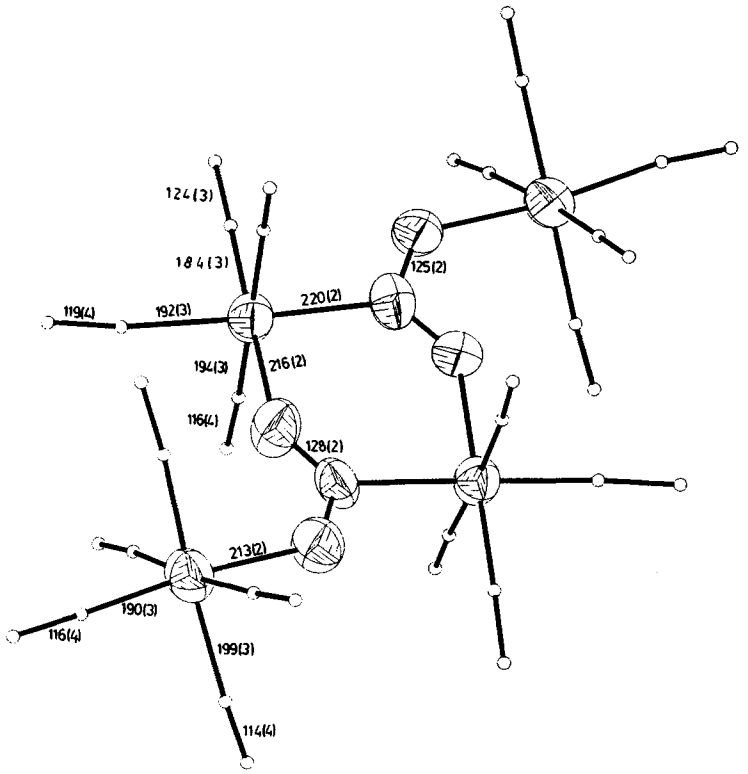
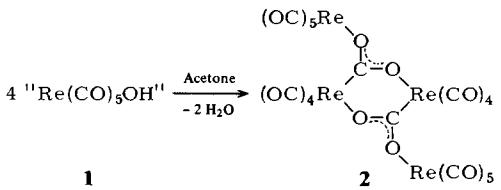
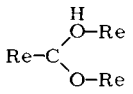


Fig. 1. Molecular structure of complex **2** in the crystal (50% probability thermal ellipsoids). The carbonyl groups are represented schematically and the given bond lengths are averages for the respective equivalent bonds. Space group $P2_1/c$, $a = 1402.3(6)$, $b = 1121.8(4)$, $c = 1954.2(5)$ pm, $\beta = 92.83(3)°$, $\rho_{calc} = 2.89$, $\rho_{exp} = 2.87$ (± 0.05) g·cm^{-3}, $Z = 4$; 4392 reflections ($I > 1.5\sigma(I)$), 215 parameters (measurement: Syntex P3, solution: Shel XTL), $R_1 = 0.084$.

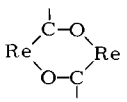
The trinuclear complex $Re_3(CO)_{14}COOH$ with the structural element



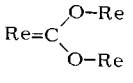
1 **2**



has recently been isolated[4]. As in this compound, the $ReCO_2$ moiety in **2** is planar. The entire six-membered ring



is also almost planar. The CO distances of the CO_2 group correspond to those in the carboxylate anion, and the Re—C bond is almost a σ single bond; hence, **2** can best be considered as a metal carboxylate. A carbene structure



has little weighting. In the $Re(CO)_4$ and $Re(CO)_5$ moieties a shortening of the Re—C bond and a lengthening of the CO bond *via* the *trans*-sited donor atoms of the CO_2 group can clearly be recognized.

2 is of interest since it represents a novel type of coordination of carbon dioxide in CO_2 complexes[5]. For the CS_2 ligand, for which numerous types of coordination are known[6], covalent bridging of three metal atoms has, to the best of our knowledge, not been observed to date.

The bond between a carbonylrhenium group and oxygen donors is apparently very stable, and we were able to obtain the very stable complexes $(OC)_5ReOCHO$, $(OC)_5Re(O_2CCO_2)Re(CO)_5$, $(OC)_5Re(C_4O_4)Re(CO)_5$, $(OC)_5ReONO$, $(OC)_5ReNO_2$ (mixture of isomers) and $(OC)_5ReONO_2$ by allowing $(OC)_5ReFBF_3$ to react with formate, oxalate, squarate, nitrite, and nitrate, respectively.

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Constitution of the Deferriform of the Albomycins δ_1, δ_2, and ε**

By *Günter Benz*, Theo Schröder, Jürgen Kurz, Christian Wünsche, Wolfgang Karl, Gerd Steffens, Jörg Pfitzner,* and *Delf Schmidt*

Dedicated to Professor Grünewald on the occasion of his 60th birthday

From the strain *Streptomyces spec.* WS 116 (DSM 1692) three sulfur-containing antibiotics were isolated whose physico-chemical properties were identical in all respects with those of the albomycins δ_1, δ_2, and ε isolated by *Maehr et al.*[2].

The constitution published in 1965[5] (ferriform) for the albomycin δ_2 was later thrown into doubt[2,6].

According to our spectroscopic investigations (CD, UV, MS, ^{1}H-NMR, ^{13}C-NMR) albomycin δ_2 has the constitution **2a**. Mild basic hydrolysis (pH = 8—9, 90 °C, 2 h) of **2a** leads to formation of the albomycins ε and δ_1, which according to their UV spectra have the constitution **2b** and **2c**, respectively.

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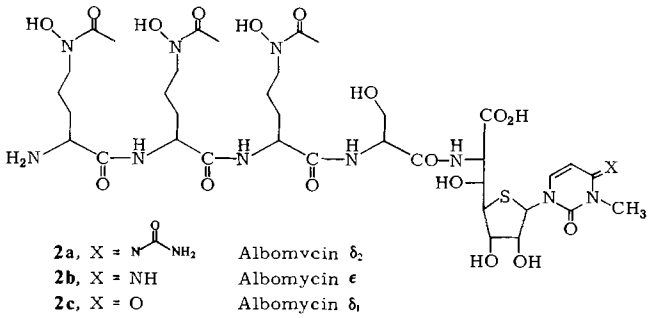
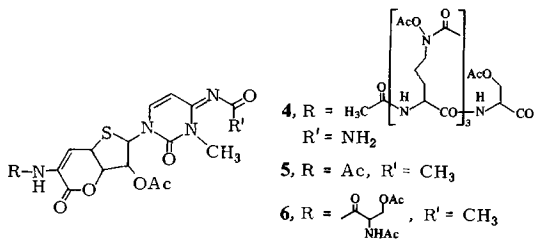


2a, X = N(C=O)NH$_2$ Albomycin δ_2
2b, X = NH Albomycin ϵ
2c, X = O Albomycin δ_1

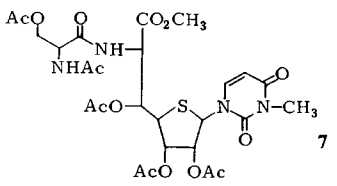
The following experiments and observations support the quoted constitutions **2a**—**2c**:

1) According to the Moore-Stein analysis the ornithine : serine ratio is 3 : 1[2]; the sequence of the open-chain peptide was determined by Edman degradation.

2) The N^4-substitution in the pyrimidine moiety of albomycin δ_2 can probably be made by comparison of the UV [(0.1 N HCl) $\lambda_{max} = 304$ nm and ^{13}C-NMR spectra with those of N^4-carbamoyl-1,3-dimethylcytosine: both compounds show the same longwave UV absorption and a ^{13}C-NMR signal at $\delta = 168$, which is assigned to the urea carbonyl-C atom.



4, R = H_3C, R' = NH_2
5, R = Ac, R' = CH_3
6, R = NHAc, R' = CH_3



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3) The constitution of the nucleoside moiety is proven by the peracetate of the albomycin δ_2, **4**, and the derivatives **5**—**7**, whose constitution is confirmed by UV, ^{1}H-NMR and MS spectra and, in the case of **4**—**6** by ^{13}C-NMR spectra. The ^{1}H-NMR spectra indicate the furanose form. The 4'-thiofuranose partial structure follows from a comparison of the mass spectrum of **5** (fragment *m/z* 223, high resolution $C_9H_9N_3O_2S$; base + C_2HS)[10] and of the ^{13}C-NMR spectrum of **4** with the corresponding spectra of 4'-thiocytidine[11]. The nucleoside-peptide coupling is proven by the serine-containing nucleosides **6** and **7**.

Mass spectra of the whole molecule are obtained only by the fast atom bombardment (FAB) technique[12]. The $(M+H)^{\oplus}$ mass lines of albomycin δ_2 (*m/z* 993) and δ_1 (*m/z* 951) confirm the proposed constitutions **2a** and **2c**, respectively.

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CAS Registry numbers:
2a, 82113-67-5; **2b**, 82113-68-6; **2c**, 82113-69-7; **3**, 82113-70-0; **4**, 82135-28-2; **5**, 82113-71-1; **6**, 82113-72-2; **7**, 82113-73-3; **10**, 82113-74-4.

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$HF \rightarrow CH_2^{\odot\oplus}$: A Novel, Stable Ion-Dipole Complex**

By *Herman Halim, Bernhard Ciommer,* and *Helmut Schwarz**

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

Unusual molecules, which because of intermolecular reactions are inaccessible in the condensed phase, can be generated and studied in an ideal way in the gas phase[1]; this applies particularly to ions, whose inherent properties can only be determined experimentally in the gas phase[2]. We report on the first complex of $CH_2^{\odot\oplus}$ with a fluorine derivative. Dissociative ionization of fluoroacetic acid **1** in the gas phase (electron impact ionization, 70 eV) affords, *via* elimination of CO_2, an ion *m/z* 34 (CH_3F) whose collisional activation (CA) mass spectrum differs characteristically from that of $CH_3F^{\odot\oplus}$ **2**, which in turn was generated by ionization of fluoromethane (cf. Table 1). Of the many alternative species $[\mathbf{1} - CO_2]^{\odot\oplus}$ of **2** we propose structure **3**, which provides an explanation why the $[M - CO_2]^{\odot\oplus}$ ions from **1**, in contrast to **2**, do not give signals for $CH_3^{\oplus}$ under CA conditions but those for $HF^{\odot\oplus}$ and very intense signals for $CH_2^{\odot\oplus}$[3].

Table 1. Collisional activation mass spectra of *m/z* 34 for $CH_3F^{\odot\oplus}$ **2** and the $[M - CO_2]^{\odot\oplus}$ ion **3** for CH_2FCO_2H **1** [a].

m/z	**2**	**3**
32	100	100
31	15.8	36.9
20 ($HF^{\odot\oplus}$)	—	1.8
15 ($CH_3^{\oplus}$)	0.4	—
14 ($CH_2^{\odot\oplus}$)	2.1	22.3
13	0.6	3.8

[a] The intensities expressed as % are relative to the base peak = 100%. In the CA spectra of **2** and **3** an intense fragment also occurs at *m/z* 33, which however—in contrast to all the other CA fragments—is also formed by unimolecular dissociation of *m/z* 34.

Molecular orbital calculations at the MNDO[4a] and *ab initio* levels (4—31G/STO-3G[4b]) support our interpretation. **2** and **3** exist in potential minima, whereby the ion-dipole complex **3** is calculated by both methods to be the more stable. Experience with calculations on other ion-dipole complexes[5a] indicates that the *ab initio* results are more reliable, although it cannot be excluded that the use of a 6—31G* basis set would reduce the discrepancy between MNDO- and 4—31G/STO-3G results[5a].

The MNDO and STO-3G geometric data (Scheme 1 contains the MNDO values, bond-lengths [Å], and angles [°]) are very similar in **3**; the only difference involves the

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Table 2. Calculated enthalpies of formation (MNDO, kcal/mol), total energies (in Hartrees), and relative energies (kcal/mol) for $CH_3F^{\oplus\ominus}$ **2** and $HF{\rightarrow}CH_2^{\oplus\ominus}$ **3**.

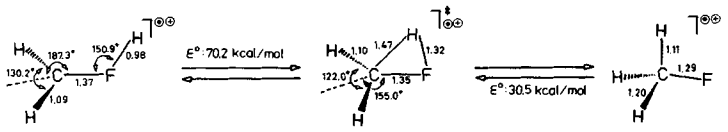
	MNDO	4–31G/STO-3G [a]	
	ΔH_f^0	E_{tot}	E_{rel}
2	223.2	−138.429312	7.1
3	183.5	−138.440611	0

[a] 4–31G/STO-3G indicates complete optimization of geometry at an STO-3G-level and single point energy calculation using 4–31G.

C—F bond lengths (according to STO-3G, 1.47 Å). Comparison of the data for **3** with that for **2**, $CH_2F^{\oplus\ominus}$, and HF leads to the following interpretation: **3** is a slightly bent complex of $CH_2^{\oplus\ominus}$ with HF, in which the C—F bond is formed by interaction of an empty sp^2-hybridized orbital of $CH_2^{\oplus\ominus}$ with one of the nonbonding electron pairs of HF; it is approximately 0.08 Å longer than the C—F bond in **2**. The C—H and F—H bond lengths in **3** are hardly (<0.01 Å) different from those in $CH_2^{\oplus\ominus}$ and HF.

Complex formation does, however, have a considerable effect on the charge distribution; whereas in $CH_2^{\oplus\ominus}$ 60% of the charge is located on the carbon atom and 20% on each of the hydrogen atoms, only 14% of the charge is located on the carbon atom in **3**. The greatest amount of charge is distributed on the hydrogen periphery: the H atom of the HF component accepts 49%, whereas each of the H atoms carry 16%; the F atom only accepts 4%. The unpaired electron of radical cation **3** is, on the whole, localized in a carbon atom $2p_y$ orbital. Complexation of $CH_2^{\oplus\ominus}$ with HF provides a stabilization of at least 43 kcal/mol (estimated from the known experimental ΔH_f^0 values of **2**, $CH^{\oplus\ominus}$, and HF assuming that **3** is at least 7 kcal/mol more stable than **2**).

That **2** and **3** exist as discrete, non freely-interconverting species, follows directly from the MNDO barrier for [1,2]-H migration: the transition state **4** (one and only one negative eigenvalue of the force-constant matrix) lies approximately 70.2 and 30.5 kcal/mol higher than **3** and **2**, respectively. Therefore, if **2** and **3** are generated, they should be considered as stable isomers, which according to their spectral data (*e.g.* the CA spectra) must be distinguishable. This is exactly what is observed (Table 1). The existence of **3** and other more stable ion-dipole complexes $X{\rightarrow}CH_2^{\oplus\ominus}$ ($X=CH_3Cl$[5a], $CH_2=O$[5b], H_2O, H_2S, HCl, and HBr[6c]), which are in part, however, only obtainable *via*



3 **4** **2**

Scheme 1

more complicated and less efficient routes, indicates that a general structural type is involved: the high stability and formally straightforward mode of formation (complexation of the ubiquitous $CH_2^{\oplus\ominus}$ with polar neutral molecules) indicate that this could be significant also in interstellar processes.

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[3] In the CA spectrum of the $[M-CO_2]^{\oplus\ominus}$ ion generated from CH_2FCO_2D, the signal for *m/z* 20 ($HF^{\oplus\ominus}$) is displaced to *m/z* 21 ($DF^{\oplus\ominus}$), whereas the signal for *m/z* 14 ($CH_2^{\oplus\ominus}$) experiences no mass shift. This result also is consistent only with one structure $DF{\rightarrow}CH_2^{\oplus\ominus}$ **3'**.

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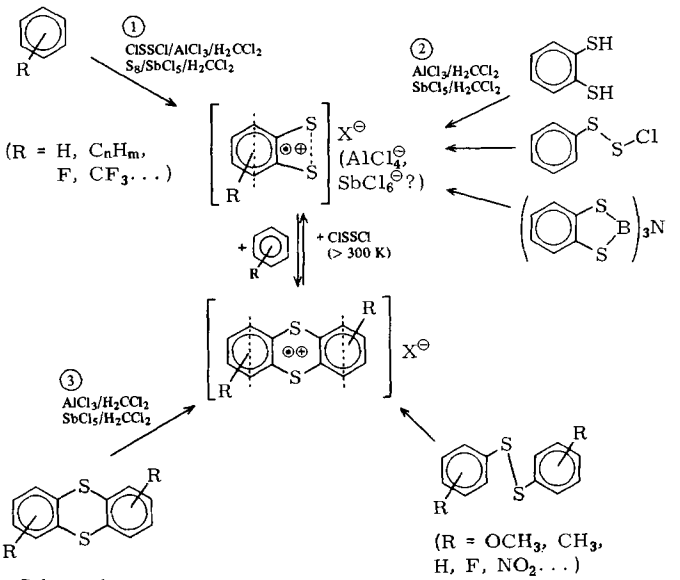
Electron Spin Resonance Studies of the Sulfur Catalysis of the Industrial Dichlorination of Benzene**

By *Hans Bock**, *Udo Stein*, and *Peter Rittmeyer*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

In the dichlorination of benzene in suspensions with 1.5% $FeCl_3$ it is known[1] that the addition of sulfur (or sulfur compounds such as dichlorodisulfane or thianthrene[2]) considerably improves the selectivity: the yield of 1,4-dichlorobenzene increases from 47% to approximately 75% and that of the *ortho*-isomer decreases from 37% to *ca.* 22%[1,2].

The conditions of the industrial chlorination suggest a radical cation intermediate. ESR spectroscopy with its high sensitivity, (concentration *ca.* 10^{-5} M, temperatures up to 180 K) therefore offers a possibility of obtaining information on the course of the sulfur-catalyzed, selective dichlorination of benzene. Preliminary results are summarized in Scheme 1:



Scheme 1

1. If dichloromethane solutions of benzene, or its alkyl- or fluoro-derivatives containing two *ortho*-hydrogens at

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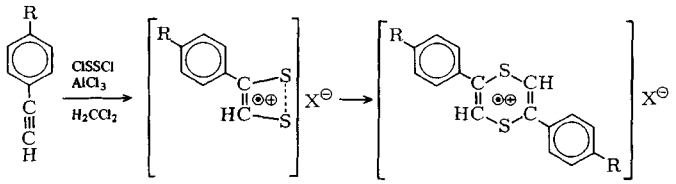
180–200 K are treated with S_2Cl_2 and $AlCl_3$ or with S_8 and $SbCl_5$, the ESR spectra of the radical cations generated, displaying hyperfine structural details, are observed. Based on ^{33}S, ^{13}C, and ^{2}H isotopic labeling, the parent compound (R = H) can be assigned a structure with C_{2v} symmetry: Presumably a ring-closed benzodithiete radical cation is present in solution. Upon warming to room temperature, the known[2] ESR signals of stable thianthrene radical cations appear in addition at high field (R = H: $g = 2.0153 \rightarrow 2.0084$).

2. Oxidation of numerous benzene derivatives[2]—1,2-benzenedithiol, chloro(phenyl)disulfane, and tris(1,3,2-benzodithiaborolyl)amine are shown as examples in Scheme 1—using the tested anhydrous and oxygen-free oxidation systems $AlCl_3/H_2CCl_2$[3b] or $SbCl_5/H_2CCl_2$[3a] also results in solutions in which the ESR signals of the unknown *o*-phenylenedithio radical cation and of the known thianthrene radical cation can be measured.

3. The oxidation of thianthrene and diphenyldisulfanes bearing the same substituents led in each case to identical thianthrene radical cations[2,3]. Addition of dichlorodisulfane and increasing the temperature result in the appearance of additional ESR signals of the substituted *o*-phenylenedithio radical cations.

Information on the preferred 1,4-dichlorination of benzene can be drawn from the ESR result that no signals are observed for substituents R in the "nodal planes" indicated in Scheme 1 by dotted lines, i.e. only a small positive charge and hence the highest electron density for an electrophilic attack is found here[2,3].

Gas phase pyrolyses, optimized by photoelectron spectroscopy[2]—*e.g.* the cleavage of propene from 2-methyl-2,3-dihydro-1,4-benzodithiane—suggest that benzodithiete can be isolated preparatively[4] and hence its chlorination investigated. Further ESR experiments with the aim of detecting reactive sulfur species, such as $ClSS^{\oplus}AlCl_4^{\ominus}$, *via* their reaction products show that the oxidation in presence of sulfur can also be applied to other π-systems. For example under the conditions shown in Scheme 1, substituted phenylacetylenes do not react to give *o*-phenylenedithio and thianthrene radical cations, but[2,4] to 3-phenyl-1,2-dithiete and further to 2,5-diphenyl-1,4-dithiin radical cations.



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[3] For generation of sulfur and silicon radical cations cf. *e.g.* a) H. Bock, G. Brähler, D. Dauplaise, U. Henkel, J. Meinwald, W. Schulz, R. Schlecker, D. Seebach, A. Semkow, U. Stein, *Chem. Ber.* 113 (1980) 289, 3280; 114 (1981) 2622, 2632; b) H. Bock, W. Kaim, *Acc. Chem. Res.* 15 (1982) 9.

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The Molecular Structure of Gaseous Titanium Tris(tetrahydridoborate) as Determined by Electron Diffraction**

By *C. John Dain, Anthony J. Downs**, and *David W. H. Rankin*

The tetrahydridoborate group is remarkable for the versatility of its ligation to metal centers which may entail triple[1a], double[1a], or even single[1b] hydrogen bridges. To date direct methods of structural analysis have been applied to only one gaseous molecule in which the tetrahydridoborate groups function as tridentate ligands, namely zirconium tetrakis(tetrahydridoborate), $Zr(BH_4)_4$[1c]. Here we wish to report the structure of the gaseous titanium tris(tetrahydridoborate) molecule which we have deduced by analyzing its electron diffraction pattern. The results have added significance in view of the dearth of structural information about molecular titanium(III) derivatives with a trigonal disposition of ligands around the metal atom.

$Ti(BH_4)_3$ was prepared by the passage of a slow stream of $TiBr_4$ vapor through a bed of powdered, freshly recrystallized $LiBH_4$ held at room temperature, the volatile products being removed under continuous pumping and trapped at 77 K. Fractionation *in vacuo* gave samples of $Ti(BH_4)_3$ which were judged to be pure on the evidence of analysis (*via* methanolysis) and of the IR[2a] and UV photoelectron[2b] spectra of the vapor; the preparative procedures previously reported[3] appear, by contrast, to have yielded only impure products. The purified product is a green solid highly susceptible to attack by traces of oxygen or moisture and with a vapor pressure at room temperature in the order of 1 torr; changes in the color and IR spectrum of the solid at lower temperatures imply the existence of more than one solid phase.

The electron diffraction pattern of gaseous $Ti(BH_4)_3$ at room temperature was measured photographically using the Edinburgh/Cornell gas-diffraction apparatus[4] over a range of 22–140 nm^{-1} (scattering variable s). Since the IR and UV photoelectron spectra of the vapor were found to exhibit the patterns characteristic of tri-hydrogen bridged tetrahydridoborate ligands[2a–c], we based the analysis of the electron scattering pattern on a model of the type $Ti[(\mu\text{-}H)_3BH]_3$ involving five independent geometrical parameters and five amplitudes of vibration; data reduction[4b] and least-squares refinement[5a] followed established procedures. Convergence of the structural refinement proceeded satisfactorily, the optimum refinement achieved to date corresponding to $R_G = 0.051$ ($R_D = 0.037$).

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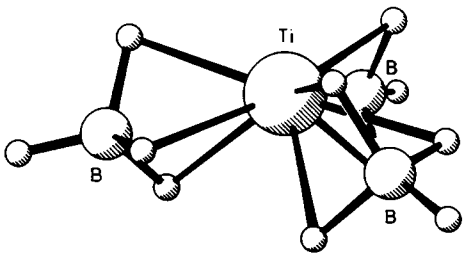

Fig. 1. Molecular structure of gaseous $Ti(BH_4)_3$. The distances correspond to r_a. The sixth parameter is the semi-vertical angle subtended by the Ti—B bonds with respect to the C_3 axis.

Parameter	Bond distance [pm] Bond angle [°]	Amplitude [pm]
r(Ti—B)	221.8(1.5)	9.8(1.2)
r(Ti—H_b)	206.7(1.7)	8.5(2.0)
r(B—H_b)	123.0(0.8)	4.5(1.9)
r(B—H_t)	110.7(2.1)	4.5 tied to u(B—H_b)
r(B···B)	375.8(1.5)	9.1(1.4)
angle	78.0(1.6)	

The two most notable features of the structure of gaseous $Ti(BH_4)_3$ (Fig. 1) are: (i) the triply bridged BH_4 groups generating ninefold coordination of the titanium atom and (ii) the non-planar geometry of the TiB_3 skeleton in which the Ti—B units depart by about 12° from a planar configuration to give a B—Ti—B angle of 115.8(0.7)°. In other respects the structural features resemble those deduced for the $Zr(BH_4)_4$ molecule[1c]. Although the departure from planarity could be an artifice of shrinkage effects, we have reasons for believing it to be an authentic feature of the equilibrium geometry of $Ti(BH_4)_3$. Thus, the molecule naturally invites comparison with $Al(BH_4)_3$, which appears on the evidence of its electron diffraction pattern to contain bidentate BH_4 groups completing a *planar* AlB_3 skeleton[5b]; unless the vibrational properties of $Al(BH_4)_3$ and $Ti(BH_4)_3$ are very different, the electron diffraction patterns admit little alternative to the conclusion that the geometries of the AlB_3 and TiB_3 skeletons are at variance. The same conclusion is reached from an analysis of the IR and Raman spectra of $Ti(BH_4)_3$ contained either in a noble-gas matrix at 15 K or in trichlorofluoromethane solution at *ca.* 250 K[2a]. Hence it appears that the vibrational fundamentals approximating most nearly to the Ti—B stretching modes conform to the selection rules and frequency pattern of a TiB_3 skeleton possessing not D_{3h} but C_{3v} symmetry. Whether the shallow pyramid of the TiB_3 skeleton stabilizes the odd electron by permitting it to be accommodated in a molecular orbital derived from the blending of $3d_{z^2}$ and $4p_z$ AO's of the titanium must at this stage be a matter of speculation; on the other hand, preliminary extended Hückel MO calculations give no grounds for anticipating anything but a planar TiB_3 skeleton[2d].

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$[Mo_4(NO)_4(S_2)_6O]^{2-}$, A Novel Highly Symmetric Polynuclear Complex with Two "Handle-Shaped" and Four "Roof-Shaped" Coordinated S_2^{2-} Bridging Ligands at a Tetragonal Mo_4 Disphenoid**

By *Achim Müller**, *Werner Eltzner*, *Hartmut Bögge*, and *Sabyasachi Sarkar*

Molybdenum-sulfur chemistry is full of surprises. This applies in particular, to complexes with S_2^{2-} ligands[1a,c]. Thus, for example, in $[Mo_4(NO)_4(S_2)_5S_3]^{4-}$ **1** it is noticeable that the S atoms are found in five different bonding states[1a,c] (structural data in [1c]).

In the complex $[Mo_4(NO)_4(S_2)_6O]^{2-}$ **2**, which we have now isolated, a (metal)$_4$aggregate (tetragonal disphenoid) is linked *via* a novel bridging system. Indeed, **2** has a very similar stoichiometry to **1**, but has, however, a completely different structure (cf. Fig. 1) with two other types of S_2^{2-} ligands (among which the "handle-shaped", previously found only in one complex[2]). Consequently, **1** and **2** contain four (!) different types of S_2^{2-} ligands (cf. [3]).

The isostructural compounds $(NH_4)_2[Mo_4(NO)_4(S_2)_6O]\cdot 2H_2O$ **2a** and $NH_4K[Mo_4(NO)_4(S_2)_6O]\cdot 2H_2O$ **2b** can be obtained by passing H_2S through an aqueous alkaline solution which contains the reaction product of MoO_4^{2-} and $NH_2OH\cdot HCl$ (unidentified hydroxylamine complex).

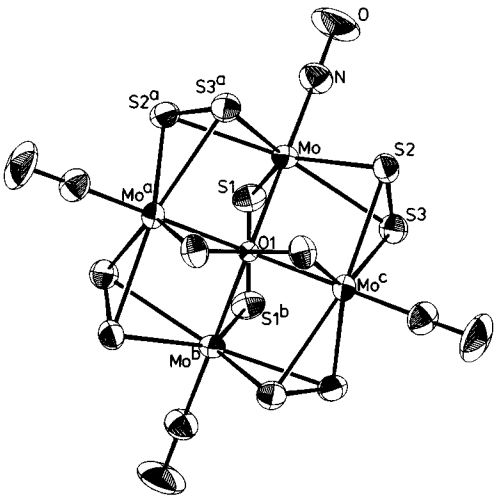

Fig. 1. Molecular structure of **2** in crystals of **2a** and **2b** (S2—S3 ≙ "roof-shaped"; S1—$S1^b$ ≙ "handle-shaped". **2a**: Space group $I4_1/a$; $a = 10.396(3)$, $c = 22.912(5)$ Å; $Z = 4$; 1171 observed reflections; $Mo_{K\alpha}$ radiation; $R = 0.057$.

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The black crystals of **2a** and **2b** were characterized by elemental analysis, vibrational spectroscopy, magnetic measurements, as well as by X-ray crystallography.

In the anion **2** (Fig. 1) the Mo atoms form a tetragonal disphenoid (Mo—Mo (short): 3.309(1), Mo—Mo (long): 3.942(2)), over whose edges two handle-shaped (S—S: 2.079(5) and four roof-shaped S_2^{2-} ligands (S—S = 2.061(3)) are situated. An O atom (Mo—O: 2.163(1)) is located at the center. Since an NO ligand (Mo—N: 1.772(8); N—O: 1.205(10) Å; Mo—N—O: 179.0(9)°) is, in addition, coordinated to each Mo atom, every metal center has a pentagonal-bipyramidal environment. **2** is diamagnetic and has the electronic configuration $\{MoNO\}^4$. The 18 electron rule is formally fulfilled for Mo if each bond to the other ligands provides an electron pair. It should be noted that the anion **2**, despite its construction from four kinds of atoms, has the high S_4 symmetry. Comparison of the structures of **1** and **2** indicates that due to steric effects, the μ_4-S atom in **1** is located outside, and the μ_4-O atom in **2** inside the Mo_4 system.

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CAS Registry numbers:
2a, 82168-21-6; **2b**, 82168-20-5; Na_2MoO_4, 7631-95-0.

[1] Cf. a) Review article: A. Müller, E. Diemann, R. Jostes, H. Bögge, *Angew. Chem. 93* (1981) 957; *Angew. Chem. Int. Ed. Engl. 20* (1981) 934; c) A. Müller, R. G. Bhattacharyya, W. Eltzner, N. Mohan, A. Neumann, S. Sarkar in H. F. Barry, P. C. H. Mitchell: *Proc. 3rd Int. Conf. Molybdenum*, Climax Molybdenum Company, Ann Arbor, 1979, p. 59 (with experimental details for the preparation of numerous S_2^{2-} complexes).

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[3] Cf. also A. Müller, W. Jaegermann, *Inorg. Chem. 18* (1979) 2631; A. Müller, W. Jaegermann, J. H. Enemark, *Coord. Chem. Rev.*, in press.

Formation of Metal-Metal Bonds and Conversion of the Metal Aggregate $\{Mo_4(S_2)_4(S_2')_2\}$ by Atom-Transfer and Redox Reactions at Nonequivalent Ligands; $[Mo_4S_4(NO)_4(CN)_8]^{8-}$ an Anion with a Central Cubane-Like Unit**

By *Achim Müller**, *Werner Eltzner*, *William Clegg*, and *George M. Sheldrick*

Reactions of molybdenum-sulfur compounds with CN^- have been discussed in connection with the evolution of Mo enzymes[1] and general prebiotic problems[2]; the reaction of Mo-η-S_2^{2-}-groups is of bioinorganic interest[3]. Thio(cyano)metalates were possibly important in chemical evolution[2].

We report here on the reactions of nonequivalent S_2^{2-} bridging ligands in the tetranuclear anion $[Mo_4(NO)_4(S_2)_4(S_2')_2O]^{2-}$ **1**[4]. The Mo in **1** form a tetragonal disphenoid (without Mo—Mo bonds) with two bridging "handle-shaped" and four "roof-shaped" S_2^{2-} ligands. **1** reacts with KCN to give red crystalline $K_8[Mo_4S_4(NO)_4(CN)_8]\cdot 4H_2O$ **2** in low yield[5], which contains the cubane-like cluster anion **3**. Atom-transfer and redox processes are involved in this reaction, whereby two Mo—Mo bonds are formed. **2** was characterized by crystal structure analysis (Fig. 1), magnetic measurements, as well as by IR, Raman, and XPS spectroscopy.

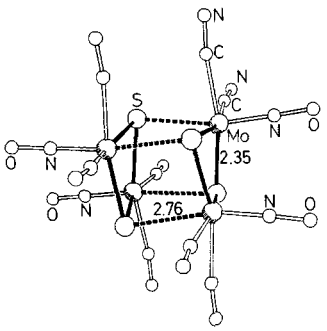
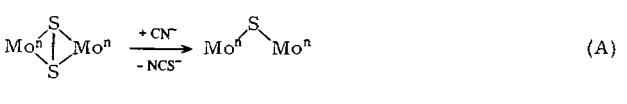


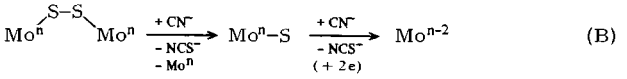
Fig. 1. Structure of **3** in crystals of **2**. Space group $P4_2/nmc$; $a = 12.333(6)$, $c = 11.553(4)$ Å; $Z = 2$; 864 reflections with $F > 4\sigma(F)$; $R = 0.060$ ($R_g = 0.056$). **3** adopts a special position with point symmetry D_{2d} ($\bar{4}2$ m) and has three orientations in the lattice.

Each Mo atom of the central Mo_4S_4 system in **3** is coordinated by one NO ligand (Mo—NO = 1.76(2)) and two CN^- ligands (Mo—CN = 2.21(2)). The Mo—S bonds (2.76(2)) *trans* to NO are considerably longer than those in the *cis*-positions (2.35(2)), and hence the central unit of **3** can also be described as two linked Mo_2S_2 quadrilaterals with metal-metal bonds (Mo—Mo = 2.99(3); Mo—Mo (long *i.e.* between the two units = 3.67(4) Å). The values given are averages (with estimated standard deviations) for the three disordered positions of **3**. The large negative charge of the diamagnetic anion **3** produces a high electron density on the NO ligands and, hence, an extremely low ν(NO) frequency (1450 cm^{-1} in KBr disc) is observed.

Apart from **3** there are only few polynuclear nitrosyl complexes. Of particular note is the reaction of **1** containing the $\{Mo_4(S_2)_4(S_2')_2\}$ moiety to yield **3** containing the Mo_4S_4 unit. The four "roof-shaped" S_2^{2-} ligands probably react as in (A) (without changing the oxidation staten of



(A)



(B)

Mo) and the two "handle-shaped" as in (B)). In addition, reaction (B) (reduction of two Mo centers by formal addition of 2·2 electrons) leads to the formation of two Mo—Mo bonds. After S transfer as in (A) the bridging S^{2-} ligand of the MoSMo linkage is, as expected, inert towards further nucleophilic attack by CN^-. The trivalency of the sulfur (as originally in the "roof-shaped" ligands) is then

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re-established by formation of a further Mo—S bond, which leads to a pseudocubane structure.

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CAS Registry numbers:
2, 82182-28-3; $(NH_4)_2[Mo_4(NO)_4(S_2)_4(S_2^{2-})_2O]$, 82168-22-7.

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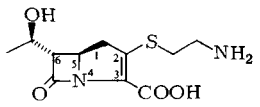
[4] A. Müller, W. Eltzner, H. Bögge, S. Sarkar, *Angew. Chem. 94* (1982) 555; *Angew. Chem. Int. Ed. Engl. 21* (1982), 535.
[5] The main product is a yellow species (very probably the less interesting binuclear complex $[Mo_2(NO)_2S_2(CN)_6]^{6-}$ with an additional CN^- ligand *trans* to NO), which is not obtained using the preparative procedure described for **2** because of its higher solubility.

1-Acetoxycarbapenems

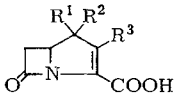
By *Wolfgang Koller, Adolf Linkies, Hartmut Pietsch, Herbert Rehling,* and *Dieter Reuschling**

Dedicated to Professor Weissermel on the occasion of his 60th birthday

Since the discovery of thienamycin **1**[1] numerous 1-unsubstituted carbapenem derivatives have been synthesized[2]; in contrast, little is known about 1-substituted systems **2**[3]. We report here on a simple method for the preparation of 1-acetoxycarbapenems.



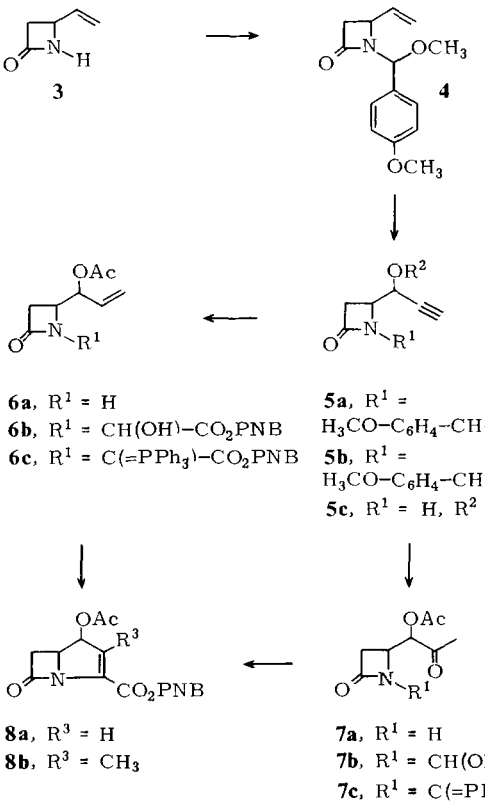
1



2

R^1, R^2 = Alkyl, O, H/O—Acyl; R^3 = H, Alkyl

4-Vinylazetidin-2-one **3** is converted into the *N*-protected compound **4** (77%), which is then subjected to ozonolysis in CH_2Cl_2/CH_3OH (2:1); after reductive work-up the resulting hemiacetal of the 4-formylazetidin-2-one is allowed to react with lithium acetylide. The hydroxyalkynyl compound **5a** (56%) is isolated as the acetate **5b** (55%). Deblocking leads to the azetidin-2-one **5c** (89%), which can be hydrogenated to **6a** (82%) and hydrated to give **7a** (80%). The glyoxylic acid derivatives **6b** and **7b** were prepared from **6a** and **7a** in 81% and 63% yield, respectively (PNB = *p*-nitrobenzyl). Conversion of **6b** and **7b** into the phosphoranes **6c** (60%) and **7c** (87%) was accomplished by the usual methods ($SOCl_2/NEt_3$; Ph_3P/NEt_3). Ozonization of the phosphorane **6c** in the presence of trifluoroacetic acid[9] followed by reductive work-up and neutralization directly afforded the carbapenem **8a** (52%). The intramolecular Wittig-reaction of the ketone **7c**, on the other hand, required much more severe conditions: 32 hours' heating in toluene in presence of propylene oxide led to **8b** (53%). All attempts to cleave the *p*-nitrobenzyl esters **8a** and **8b** hydrogenolytically led to pyrrole derivatives, and not to the expected acids.



3, **4**

6a, R^1 = H
6b, R^1 = CH(OH)—CO_2PNB
6c, R^1 = C(=PPh_3)—CO_2PNB

5a, R^1 = H_3CO—C_6H_4—$CH(OCH_3)$, R^2 = H
5b, R^1 = H_3CO—C_6H_4—$CH(OCH_3)$, R^2 = Ac
5c, R^1 = H, R^2 = Ac

8a, R^3 = H
8b, R^3 = CH_3

7a, R^1 = H
7b, R^1 = CH(OH)—CO_2PNB
7c, R^1 = C(=PPh_3)—CO_2PNB

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CAS Registry numbers:
3, 7486-94-4; **4**, 82113-75-5; **5a**, 82113-76-6; **5b**, 82113-77-7; **5c**, 82113-78-8; **6a**, 82113-79-9; **6b**, 82113-80-2; **6c**, 82113-81-3; **7a**, 82113-82-4; **7b**, 82113-83-5; **7c**, 82113-84-6; **8a**, 82113-85-7; **8b**, 82113-86-8; 4-formylazetidin-2-one hemiacetal, 82113-87-9.

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[2] See *e.g.* Minoru Hatanaka, Yu-ichi Yamamoto, Hajime Nitta, Toshijasu Ishimaru, *Tetrahedron Lett. 1981*, 3883, and references cited therein.
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[9] J. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, R. B. Woodward, *J. Am. Chem. Soc. 100* (1978) 8214.

Functionalization of α-Methylenecarbonyl Compounds to β-Acetoxyphosphane Oxides and Vinylphosphane Oxides

By *Jürgen Sander**, *Hanß-Jerg Kleiner,* and *Manfred Finke*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

In our work on the functionalization of carbonyl compounds[1] we used the well-investigated[2,3] addition products of secondary phosphane oxides to olefins.

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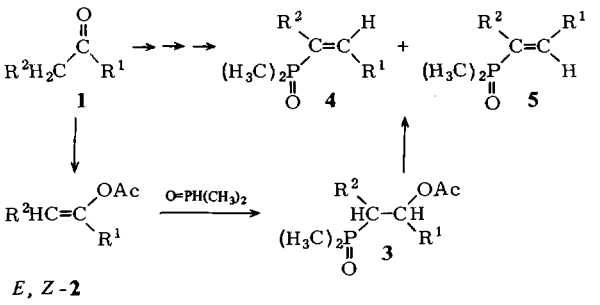
On using the enol acetates **2** as multibonding components, which are readily accessible from α-methylenecarbonyl compounds **1**, the β-acetoxyphosphane oxides **3** are obtained[2a,c].



E, Z-**2**

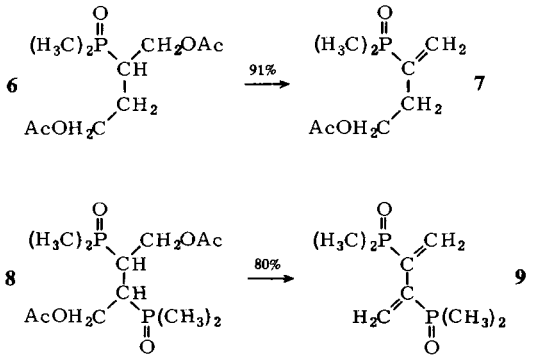
We have now found that the products **3** eliminate acetic acid on heating to 180–250 °C, and the novel vinylphosphane oxides **4** and/or **5**[4a] are formed. Table 1 shows some examples.

Table 1. Examples of the synthesized products **3** as well as **4** and/or **5**. The compounds gave correct elemental analyses.

		3 [a]		**4** and/or **5** [b]	
R^1	R^2	Yield [%]	B.p. [°C/mbar]	Yield [%]	B.p. [°C/mbar]
H	H	86 [2a]	135–140/0.5	95	[c]
CH_3	H	92 [2c]	110/0.3	92	[d][e]
—$(CH_2)_4$—		77	145/0.5	70	[d] 150–155/10
nC_3H_7	C_2H_5	77	120–135/0.05	73	140–145/10
H	nC_5H_{11}	72	135/0.3	71	135–140/8

[a] **3**: **2** (1 mol) containing 2 wt-% of di-*tert*-butyl peroxide, is added dropwise into vigorously stirred $O{=}PH(CH_3)_2$ (1 mol) under N_2 at 140–160 °C. After 2 hours' stirring at 140–160 °C, high-vacuum distillation affords, aside from **3**, sometimes also small amounts of the α-acetoxyphosphane oxide, which cannot be separated by distillation. [b] **4**/**5**: The addition product **3** obtained according to [a] is heated for 8 h at 250 °C and normal pressure. After removal of the acetic acid the residue is fractionally distilled. α-Acetoxyphosphane oxides can be separated by distillation. [c] M.p. 68–69 °C [4b]. [d] Exclusive formation of **5**. [e] M.p. 59–60 °C.

If 2-butenylene diacetate[2b] or 2-butynylene diacetate instead of the enol acetate is used as educt, β-acetoxyphosphane oxides **6** (98%[2b]) and **8** (70%, m.p. 175–178 °C), respectively, are likewise obtained. They undergo single and double elimination of acetic acid to give the novel unsaturated phosphane oxides **7** (b.p. 133–142 °C/0.004 mbar) and **9** (m.p. 120–122 °C), respectively.



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German version: *Angew. Chem.* **94** (1982) 561

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[2] a) H.-J. Kleiner, DBP 2040280 (1970), Hoechst; b) U. Dettmeier, H.-J. Kleiner, DBP 2064574 (1970), Hoechst; c) C. Beermann, H.-J. Kleiner, DOS 2133795 (1970), Hoechst.
[3] H.-J. Kleiner, *Justus Liebigs Ann. Chem.* **1974**, 751.
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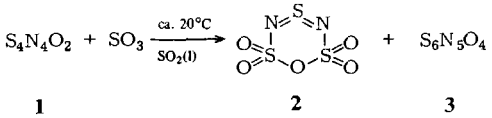
$S_6N_5O_4$, A Compound with Separately Stacked Cyclic Radical Cations $S_3N_2^+$ and Cyclic Anions $S_3N_3O_4^-$**

By *Herbert W. Roesky**, *Michael Witt*, *Jürgen Schimkowiak*, *Martin Schmidt*, *Mathias Noltemeyer*, and *George M. Sheldrick*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

Reaction of tetrasulfur tetranitride with sulfur trioxide or other Lewis acids generally leads to formation of 1:1 adducts[1]. In these compounds a nitrogen atom of S_4N_4 is bound to the electrophilic center of the reaction partner, thus changing the structure of the educt S_4N_4 (with all four nitrogen atoms in one plane) to a saddle conformation in which the sulfur atoms form an approximate square. As a consequence, the transannular sulfur-sulfur interaction in S_4N_4 is removed.

If the *S,S*-dioxide $S_4N_4O_2$[4a] **1** is allowed to react with SO_3 in the molar ratio 1:2 in liquid SO_2 the novel compound $S_6N_5O_4$ **3** (20%) is formed, as well as the well-known $S_3N_2O_5$[4b] **2** (80%).



The greenish-black crystals of **3** are extremely sensitive towards oxygen and moisture; they cannot be dissolved again without decomposition.

As shown by the X-ray structure analysis [monoclinic single crystal, space group $P2_1/n$, $a = 700.7(3)$, $b = 1216.8(4)$, $c = 1154.2(3)$ pm, $\beta = 103.61(2)°$; $Mo_{K\alpha}$ radiation, 1140 symmetry-independent reflections with $F > 4\sigma(F)$, $R = 0.0611$, $R_w = 0.0563$], **3** is composed of the $S_3N_2^+$ radical cation and the $S_3N_3O_4^-$ anion (Fig. 1). Structures containing the anion[8] and cation[5], in each case with other counter-ions, are known. In **3**, however, we observed for the first time separated stacks of anions and of radical cations.

The cations in **3** are present as loosely bound centrosymmetric dimers: two S...S distances of 294.7 pm between two radical cations are clearly shorter than the van-der-Waals distance of 350 pm. The structural makeup of **3**

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involving radical properties could serve as a model for the synthesis of electron conductors from non-metals.

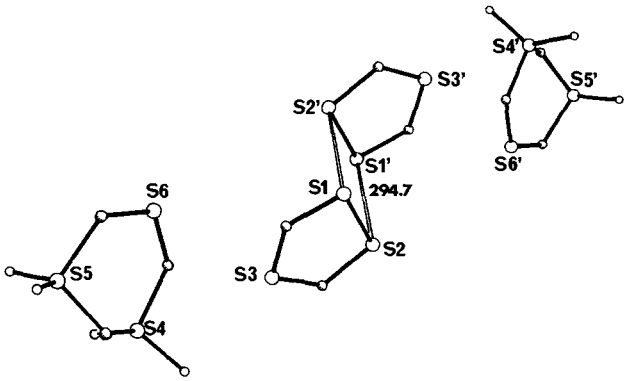

Fig. 1. Structure of compound **3** in the crystal. The most important atomic distances are (pm, standard deviations in brackets): S1—S2 215.4(3), S1(2)—N1(2) 159.8 (mean value), N1(2)—S(3) 157.8 (mean value); N4(5)—S6 154.3 (mean value), N4(5)—S4(5) 167.6 (mean value), N3—S4(5) 158.7 (mean value), S4(5)—O1(2;3,4) 142.8 (mean value).

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CAS Registry numbers:
1, 57932-64-6; **2**, 72884-15-2; **3**, 82136-25-2; SO_3, 7446-11-9.

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Photochemically Generated 1,4-Dihydroxypyridines and 2-Hydroxytetrahydropyridines as Precursors for Benzo[*a*]quinolizidine Alkaloids**

By *Lutz-F. Tietze** and *Klaus Brüggemann*

Dedicated to Professor Weissermel on the occasion of his 60th birthday

Owing to their reactivity, as a result of enamine-imine(iminium-salt) tautomerism, dihydropyridines[1] are of great importance as intermediates in the synthesis of complex nitrogen-containing natural products; besides, they are formulated as intermediates in the biosynthesis of numerous alkaloids. The 2-hydroxytetrahydropyridines, which form the corresponding iminium salts by acid-catalyzed reaction, are even more reactive. We have recently been able to show that 1,4-dihydropyridines and 2-hydroxytetrahydropyridines can be obtained by photochemical addition of enaminoaldehydes to olefins[2]; we now describe the use of this method for the synthesis of derivatives of benzo[*a*]quinolizidine, the parent compound of the ipecacuanha alkaloids.

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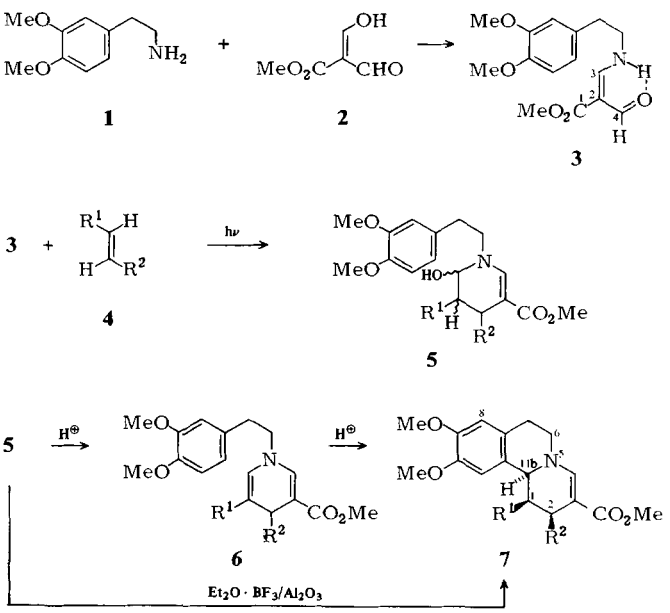
[**] Dihydropyridines, Part 2. This work was supported by Forschungsmitteln des Landes Niedersachsen.—Part 1: [2].

Condensation of 2-(3,4-dimethoxyphenyl)ethylamine **1** with methyl diformylacetate **2** (toluene, Na_2SO_4, 20 °C, 3 h) affords the enaminoaldehyde **3** in 82% yield, which at 20 °C in $CDCl_3$ is present up to 95% in the *Z-s-Z* conformation. Irradiation of a mixture of **3** (1 molar equivalent) and olefin **4a—4e** (10—100 molar equivalents) in CH_2Cl_2 ($\lambda \geq 300$ nm) at −20 °C furnishes the unstable diastereomeric 2-hydroxytetrahydropyridines **5** in the ratio 1 : 2[3]. The photochemical [2+2]-cycloaddition proceeds completely regioselectively[4]. Presumably a cyclobutane system is formed as intermediate by attack of the olefin **4** at C-2 and C-4 in **3** (cf. mesomeric resonance form/tautomer of **3**); hetero-retro-aldol cleavage then yields a new enaminoaldehyde, which recyclizes to **5**.

Olefins containing electron-acceptor groups, **4a—4d**, react with **3** to give the 2-hydroxytetrahydropyridines **5a—5d** having acceptor groups in the 4-position, while olefin **4e**, which contains a donor group, yields the 3-substituted compounds **5e**. Acid-catalyzed reaction of **5a—5d** furnishes the dihydropyridines **6a—6d**. Thus, with catalytic amounts of trifluoroacetic acid in CH_2Cl_2 at 20 °C, **5a** affords **6a** in 85% yield within a few minutes; prolonged reaction leads to the quinolizidine derivative **7a** (80%)[5].

The quinolizidine derivatives **7a—7e**[5] can, however, be synthesized much more simply by reaction of the crude tetrahydropyridines **5a—5e**[6], obtained after removal of solvent and excess olefin, with $EtO_2 \cdot BF_3$ on aluminum oxide[3] (CH_2Cl_2, 20 °C, 5 min). Primarily, the iminium salt is formed, which reacts further in a kind of Pictet-Spengler



4–7	a	b	c	d	e	f	g
R^1	H	H	CH_3	H	OMe		
R^2	CN	CO_2Me	CO_2Me	$COCH_3$	H		
Yield [%] 3→7	88	71	93	83	45	0	0

reaction. In each of the cases **7a—7e** only one diastereomer is obtained. Presumably the reaction, except for **7c** and **7e**, is thermodynamically controlled, since on reaction of **6a** the epimer of **7a** is also formed. However, on prolonged reaction this is converted into **7a**, the thermody-

namically more stable product containing a pseudoequatorial cyano group. Reaction with cyclopentene or (*Z*)-2-butene yields respectively the 2-hydroxytetrahydropyridines **5f** and **5g**, and the 1,4-dihydropyridines **6f** and **6g**; a cyclization to the benzo[*a*]quinolizidines fails, presumably on account of steric hindrance.

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1, 120-20-7; **2**, 39947-70-1; **3**, 82093-61-6; **4a**, 107-13-1; **4b**, 96-33-3; **4c**, 18707-60-3; **4d**, 78-94-4; **4e**, 109-92-2; **4f**, 142-29-0; **4g**, 590-18-1; **5a**, 82093-62-7; **5b**, 82093-63-8; **5c**, 82093-64-9; **5d**, 82093-65-0; **5e**, 82093-66-1; **6a**, 82093-67-2; **6b**, 82093-68-3; **6c**, 82093-69-4; **6d**, 82093-70-7; **6f**, 82093-71-8; **6g**, 82093-72-9; **7a** isomer I, 82093-73-0; **7a** isomer II, 82093-74-1; **7b** isomer I, 82093-75-2; **7b**, isomer II, 82093-76-3; **7c**, 82093-77-4; **7d** isomer I, 82093-78-5; **7d** isomer II, 82093-79-6; **7e** isomer I, 82093-80-9; **7e** isomer II, 82093-81-0; **7f**, 82093-82-1; **7g**, 82093-83-2.

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[2] L.-F. Tietze, K. Brüggemann, *Angew. Chem. 91* (1979) 575; *Angew. Chem. Int. Ed. Engl. 18* (1979) 540.
[3] Typical reaction conditions: A solution of enaminoaldehyde **3** (2.00 mmol) and olefin **4** (80.0 mmol) in CH_2Cl_2 (200 mL) is irradiated for 1.3—2.5 h (**3d**: 14.5 h) at −20 °C with a Hg high-pressure lamp (500 W; Hanau) in a Duran ring reactor (cf. Tietze/Eicher: *Reaktionen und Synthesen in organisch-chemischen Praktikum*, Thieme, Stuttgart 1981, p. 13). After removal of solvent and excess olefin **4** (except in the case of **4d**) the residue is taken up in CH_2Cl_2 (200 mL) and the stirred solution is treated with 200 mg of $Et_2O \cdot BF_3/Al_2O_3$ (1:2 mol-%) at 20 °C (**7e**: −60 °C → 0 °C). This previously unknown reagent gives better yields than the reaction with $Et_2O \cdot BF_3$ alone.
[4] L.-F. Tietze, A. Bergmann, unpublished results.
[5] **7d**: ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 7.62$ (s, 1 H, 4-H), 6.64 (s, 1 H, 8-H), 6.60 (s, 1 H, 11-H), 4.39 (br. d, $J = 11$ Hz, 1 H, 11b-H), 3.87 (s, 6 H, O—CH_3), 3.72 (m, 1 H, 2α-H), 3.67 (s, 3 H, O—CH_3), 3.63—3.38 (m, 2 H, 6-H), 3.02 (m, 1 H, 7-H), 2.68 (m, 1 H, 7-H), 2.46 (ddd, $J = 13$ Hz, $J = 6$ Hz, $J = 3$ Hz, 1 H, 1α-H), 2.12 (s, 3 H, CH_3), 1.72 (dt, $J = 13$ Hz, $J = 11$ Hz, 1 H, 1β-H).
[6] The diastereomeric semiaminals **5** react at various rates. Small amounts of the dihydropyridines **6** (< 1%) are also formed; these likewise cyclize to **7**, but more slowly, under the reaction conditions.

2-Oxopropanal (Methylglyoxal) by Oxidation of Glycerin in the Gas Phase

By *Herbert Baltes* and *Ernst Ingo Leupold**

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

2-Oxopropanal **2** and its acetals are important industrial intermediates, *e.g.* for the production of pyrethrum insecticides[1]. On an industrial scale, **2** is primarily produced from 1,2-propanediol[2].

A novel simple entry to **2** is the gas-phase oxidation of glycerin **1** at 300—350 °C on specially developed heterogeneous catalysts[3].
Presumably, the initial product is 1,3-dihydroxyacetone, which immediately rearranges with elimination of water to give **2**[4].

$$\underset{\mathbf{1}}{HOCH_2—CH(OH)—CH_2OH} + 1/2\,O_2 \rightarrow \underset{\mathbf{2}}{CH_3—CO—CHO} + 2\,H_2O$$

A suitable form of reactor consists of an externally heated glass tube (diameter: 2 cm; length 15 cm), arranged vertically and packed with catalyst (15 cm^3) covered by a layer of glass beads (vaporization zone). A mixture of glycerin and water is pumped into the vaporization zone from the top. The resulting vapor is mixed with pre-heated nitrogen and oxygen or air and passed through the catalyst. The residence times are 0.2 to 0.5 s. The products are condensed in a cold trap and analyzed by HPLC.

Vanadium, molybdenum, silver, and tin (in particular, combinations of vanadium and silver) are suitable as catalytically active elements. The elements are deposited from solutions of their salts onto surface area-deficient aluminosilicate supports, dried, and oxidized in a stream of oxygen[3].

Two typical examples are given in Table 1. The main byproducts and secondary products formed are acrolein, formaldehyde, and carbon dioxide.

Table 1. Oxidation of glycerin **1** to 2-oxopropanal **2** in the gas phase. Catalyst carrier: aluminosilicate (BET surface area *ca.* 1 m^2/g; water uptake 30 wt-%).

	Expt. 1	Expt. 2
Catalyst [a]	3.2% V + 6.8% Ag	5% V + 5% Ag
Reaction temperature [°C]	350	300
Molar ratio O_2 : **1**	2 : 1	2 : 1
Molar ratio H_2O : **1**	5.1 : 1	5.1 : 1
2—STY [b]	186	193
2—Selectivity [%]	55	72

[a] Data in wt-%. [b] Space-time-yield [g **2**/(dm^3 catalyst · h)].

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1, 56-81-5; **2**, 78-98-8

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[4] M. Fedoronko, J. Königstein, *Collect. Czech. Chem. Commun. 34* (1969) 3881.

2-Cyano-3-ethoxyacrylamides—Selective Synthons for the Synthesis of Heterocycles

By *Klaus-Dieter Kampe**

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

In contrast to the triacylmethanes, which are readily cleaved by nucleophiles, the 3-alkoxy-2-acylacrylic acid derivatives **1**, as capped triacylmethanes, are useful synthetic building blocks. We have now investigated some reactions of 2-cyano-3-ethoxyacrylamides **3** (*E* > *Z* mixtures or pure *E*-isomers[12]) with bisnucleophiles regarding their selectivity.

The amides **3** react with amidines **4**, **5** and guanidines **6—9** in glyme/*i*-PrOH at 82 °C to give 4-amino-5-pyrimidinecarboxamides **10—15**. The amide group remains intact during the condensation.

Unlike the amides **3**, the *E*,*Z*-ester **16** reacts with amidines non-selectively at the enol ether function and one of

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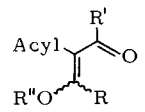
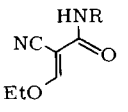
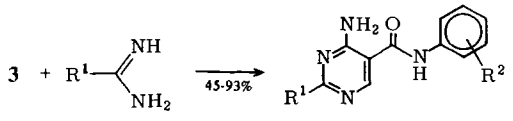


1

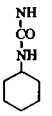


3

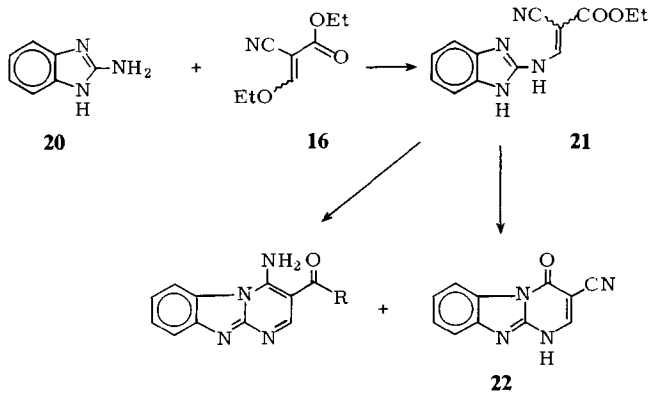
	R	
a	H	
b	4-Cl–C_6H_4	($E > Z$)
c	3-F_3C–C_6H_4	(E)
d	2-Cl,4-NO_2–C_6H_3	($E > Z$)



4-9 10-14, 15a, 15c

	4	5	6	7	8	9
	10	11	12	13	14	15
R^1	H	Ph	H_2N			
R^2	4-Cl	3-CF_3	3-CF_3	3-CF_3	3-CF_3	**a**, H instead of $C_6H_4R^2$ **c**, 3-CF_3

the two acyl groups. The formation of **22** and **23** (2.5 : 1) from **16** and **20** is well known[3]. From **16** and **20** in glyme at 75 °C, *i.e.* under conditions under which reaction of **20** with **3c** gives only **24**, we obtained almost equal amounts of **21**, **22**, and **23**.



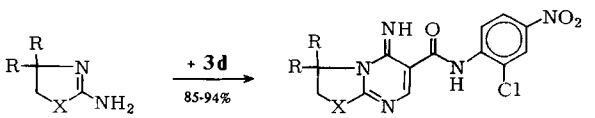
20 16 21

22

23, R = EtO

20 + 3c ⟶ (94%) **24**, R = 3-$F_3CC_6H_4NH$

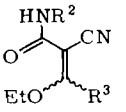
Amides (example **3d**) also react with 2-amino-2-azolines **26** and **27** to give only a single product, namely **28** and **29**, respectively.



26	X = O, R = CH_3	**28**
27	X = S, R = H	**29**

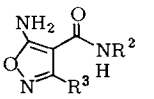
The 3-alkyl homologues of **3**, *e.g.* **30a**, react with the guanidines **6**—**9** with cleavage of R^1H to give pyrimidinones or oxazines (as yet unclear) and with benzamidine **5** to give pyrimidinones.

Compounds **3** (*e.g.* **3c**) and **30** (*e.g.* **30b**) react with hydroxylamine in ethanol/NEt_3 at 80 °C to give 5-amino-4-isoxazole-carbanilides **38** and **39**, respectively.



3c, R^3 = H (>75% *E*)
30a, R^3 = CH_3 (70% *Z*)
30b, R^3 = C_2H_5 (*Z*)

R^2 =



38, R^3 = H
39, R^3 = C_2H_5

In contrast to **16** the new 2-cyano-3-ethoxyacrylamides **3** are thus very effective, regioselectively reacting synthons for the synthesis of heterocycles with functional groups. Amino- and carbamoyl-groups, aside from other functions, can be incorporated in one step.

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CAS Registry numbers:
3a, 82113-88-0; *(E)*-**3b**, 82113-89-1; *(Z)*-**3b**, 82113-90-4; *(E)*-**3c**, 82113-91-5; *(E)*-**3d**, 82113-92-6; *(Z)*-**3d**, 82113-93-7; **4**, 463-52-5; **5**, 618-39-3; **6**, 113-00-8; **7**, 17238-58-3; **8**, 15207-76-8; **9**, 75689-92-8; **10**, 82113-94-8; **11**, 82113-95-9; **12**, 75690-63-0; **13**, 82113-96-0; **14**, 75690-44-7; **15a**, 82113-91-1; **15c**, 75689-93-9; *(E)*-**16**, 42466-67-1; *(Z)*-**16**, 42466-69-3; **20**, 934-32-7; **21**, 82113-98-2; **22**, 40752-97-4; **23**, 40752-96-3; **24**, 82113-99-3; **26**, 52832-91-4; **27**, 1779-81-3; **28**, 82135-29-3; *(Z)*-**28**, 82135-30-6; *(E)*-**29**, 82135-31-7; *(Z)*-**29**, 82135-32-8; *(E)*-**30a**, 63927-49-1; *(Z)*-**30a**, 63927-50-4; *(Z)*-**30b**, 82114-00-9; **38**, 82114-07-6; **39**, 82135-33-9.

[2] (Excerpt) The assignment was achieved on the basis of the NMR signal of 3-H and the 1,3-^1H,^{13}C coupling constant.

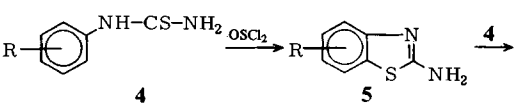
[3] A. W. Chow, D. R. Jakas, B. P. Trotter, N. M. Hall, J. R. E. Hoover, *J. Heterocycl. Chem. 10* (1973) 71.

2-Aminobenzothiazoles by Oxidative Cyclization of Arylthioureas with Sulfinyl Chloride

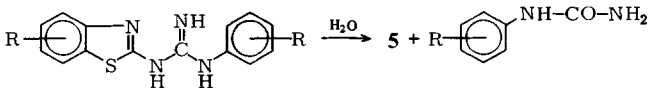
By *Theodor Papenfuhs**

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

Arylthioureas **4** can be oxidized with sulfinyl chloride. Donor-substituted educts **4** react cleanly with an excess of sulfinyl chloride in the absence of solvent to give 2-aminobenzothiazoles **5**[9]. With sulfinyl chloride used in high dilution and initially in substoichiometric amounts, and especially with acceptor-substituted educts (**4**, R = NO_2, halogen, CN, COOR) the guanidines **6** are also formed; these are cleaved by water to 2-aminobenzothiazoles **5** and arylureas **7**.



4 5



6 7

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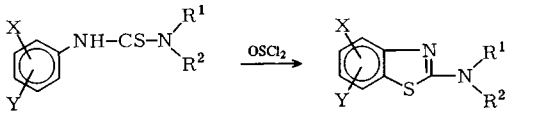
Hoechst AG
D-6230 Frankfurt am Main 80 (Germany)

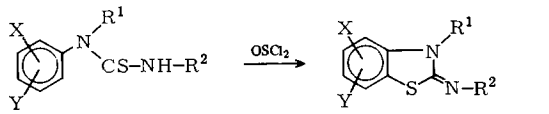
The following analytically confirmed empirical equation was determined for the solvent-free reaction of **4** with sulfinyl chloride in excess:

$$2\ \mathbf{4} + 2\ OSCl_2 \rightarrow 2\ \mathbf{5}\cdot HCl + S + SO_2 + 2\ HCl$$

In order to ascertain the scope of application of this novel entry to the benzothiazole series not only the reactions of **10** but also those of multi-*N*-substituted arylthioureas **12** and **14** were examined (Table 1-3).



10, $R^1 = R^2 = H$ **11**, $R^1 = R^2 = H$
12 **13**



14 **15**

Tables 1—3 (selected data). 2-Aminobenzothiazoles **11**, 2-(alkylamino)- and 2-(dialkylamino)benzothiazoles **13** as well as 3-substituted 2-iminobenzothiazolines **15** formed from the educts **10**, **12** and **14** by reaction with excess sulfinyl chloride (other examples [9]).

X	Y	R^1	R^2	Yield [%]	M.p. [°C]	Purity [%]
11						
H	H	—	—	95.6	130	99.6
4-CH_3	H	—	—	93.2	137	99.4
6-OC_2H_5	H	—	—	94.0	164	99.8
4-CH_3	6-CH_3	—	—	99.4	138	98.5
4-CH_3	7-Cl	—	—	86.4	207	98.2
13						
H	H	CH_3	H	94.8	137	99.7
6-CH_3	H	*p*-tolyl	H	91.9	169	99.7
H	H	CH_3	CH_3	95.0	86	96.7
4,5-benzo		CH_3	CH_3	94.1	138	97.6
15						
H	H	C_2H_5	H	96.0	85	99.6
4-CH_3	H	CH_3	H	91.3	84	98.7
H	H	C_6H_{11}	H	82.9	104	98.1
4-CH_3	6-CH_3	CH_3	H	88.8	104	97.0
H	H	CH_3	CH_3	91.5	62	98.2

General Procedure[9]

10, **12** or **14**[12] (2 mol) is added with stirring to $OSCl_2$ (5.6 mol) at 50—55 °C (2—4 h). The reaction mixture, which is usually viscous, is poured into 2 L of water, stirred for 30 min at 60—80 °C, and filtered. The filtrate is adjusted to pH 8 with 25% ammonia; **11**, **13**, and **15** respectively precipitate out and are filtered by suction at 20 °C, washed, and dried.

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CAS Registry numbers:
10 (X = Y = H), 103-85-5; **11** (X = Y = H), 136-95-8; **11** (X = 4-CH_3, Y = H), 1477-42-5; **11** (X = 6-OC_2H_5, Y = H), 94-45-1; **11** (X = 4-CH_3, Y = 6-CH_3), 64036-71-1; **11** (X = 4-CH_3, Y = 7-Cl), 78584-09-5; **13** (X = Y = R^2 = H, $R^1 = CH_3$), 16954-69-1; **13** (X = 6-CH_3, Y = R^2 = H, R^1 = *p*-tolyl), 42238-71-1; **13** (X = Y = H, $R' = R^2 = CH_3$), 4074-74-2; **13** (X, Y = 4,5-benzo, $R^1 = R^2 = CH_3$), 21431-38-9; **15** (X = Y = R^2 = H, $R^1 = C_2H_5$) 53641-17-1; **15** (X = 4-CH_3, Y = R^2 = H, R^1 = Me) 68716-43-8; **15** (X = Y = R^2 = H, $R^1 = C_6H_{11}$) 73901-10-7; **15** (X = 4-CH_3, Y = 6-CH_3, $R^1 = CH_3$, R^2 = H) 73901-12-9; **15** (X = Y = H, $R^1 = R^2 = CH_3$) 16416-95-8.

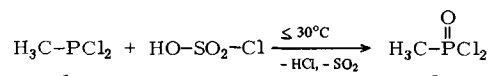
[9] T. Papenfuhs, US Pat. 4252963 (1981), Hoechst.
[12] T. Papenfuhs, Eur. Pat. 0005276 (1981), Hoechst.

Sulfuric Acid Derivatives as Oxidizing Agents for Phosphorus(III) Compounds

By *Jürgen Grosse**, *Werner Pieper*, and *Hubert Neumaier*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

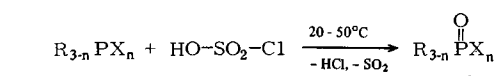
The importance of dichloro(methyl)phosphane **1** in organophosphorus chemistry has recently been outlined in a comprehensive review[1]. However, the problem of oxidizing **1** to methanephosphonic acid dichloride **2**, a versatile intermediate for organophosphorus syntheses, had previously not been satisfactorily solved.



1 **2**

Oxidation of **1** with chlorosulfuric acid[1,5] has proven superior to the conventional methods. The exothermic reaction starts spontaneously on dropwise addition of the reactants, if necessary into previously formed **2**, at room temperature with vigorous evolution of gas. After removal of the dissolved gaseous reaction products *in vacuo* highly pure **2** (>99%) is obtained in practically quantitative yield referred to chlorosulfuric acid. A purification by distillation is unnecessary.

Chlorosulfuric acid can also be used successfully for the oxidation of other phosphorus(III) derivatives to **3—13**[5].

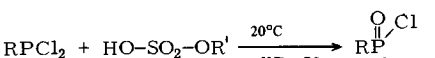


3-13

R = Alkyl, Aryl, OR', SR''; X = halogen; $n = 0-3$

Particularly good results are obtained with compounds where R = Alkyl, Aryl; X = Cl; $n = 1$ and 2 (content of product after degassing *in vacuo*, 90 to 99%; yields after distillation ≥95%).

Sulfuric acid monoesters are suitable for the oxidation of dichloro(organo)phosphanes[8] to chlorophosphonic acid esters **14—19**.



14-19

R = CH_3, C_2H_5, C_6H_5; R' = Alkyl, Aryl

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The yields are up to 60%. Apart from the phosphorus being oxidized, a chlorine atom is replaced by an ester group.

Sulfuric acid itself can also be used as oxidizing agent. The oxidation of dichloro(organo)phosphanes in ethers with conc. sulfuric acid leads to mixtures of condensed phosphonic acids **23-25** in high yields[9].

$$n\ RPCl_2 + n\ H_2SO_4 + H_2O \xrightarrow[-2n\ HCl,\ -n\ SO_2]{40^\circ C} (RPO_2)_n \cdot H_2O$$

23-25

$R = CH_3, C_2H_5, C_6H_5$

The chain length *n* is influenced to a certain extent by the amount of water present during the oxidation reaction.

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CAS Registry numbers:
1, 676-83-5; **2**, 676-97-1; **3**, 1066-50-8; **4**, 824-72-6; **5**, 1111-92-8; **6**, 1499-21-4; **7**, 10025-87-3; **8**, 7789-59-5; **9**, 18281-78-2; **10**, 115-86-6; **11**, HCl, 82113-52-8; **12**, HCl, 64990-57-4; **13**, 6609-64-9; **14**, 18359-05-2; **15**, 82113-53-9; **16**, 14235-74-6; **17**, 5284-10-6; **18**, 28829-96-1; **19**, 82113-54-0; **23**, 31985-59-8; **24**, 32146-91-1; **25**, 56410-82-3; $EtPCl_2$, 1498-40-4; $PhPCl_2$, 644-97-3; Me_2PCl, 811-62-1; Ph_2PCl, 1079-66-9; PCl_3, 7719-12-2; PBr_3, 7789-60-8; $PrSPCl_2$, 36696-24-9; $(PhO)_3P$, 101-02-0; $(Bu)_3P$, 998-40-3; $(C_8H_{17})_3P$, 4731-53-7; $(EtO)_3P$, 122-52-1; 2-chloro-1,3,2-dioxaphospholane, 822-39-9; chlorosulfuric acid, 7790-94-5; sulfuric acid monoisobutyl ester, 2412-30-8; sulfuric acid monohexadecyl ester, 143-02-2; sulfuric acid monophenyl ester, 937-34-8; sulfuric acid monethyl ester, 540-82-9.

[1] K. Weissermel, H.-J. Kleiner, M. Finke, U.-H. Felcht, *Angew. Chem. 93* (1981) 256; *Angew. Chem. Int. Ed. Engl. 20* (1981) 223.
[5] J. Grosse, DOS 3033957 (1981), Hoechst AG.
[8] J. Grosse, W. Pieper, DOS 3120069 (1982), Hoechst AG.
[9] J. Grosse, W. Pieper, patent applied for, Hoechst AG.

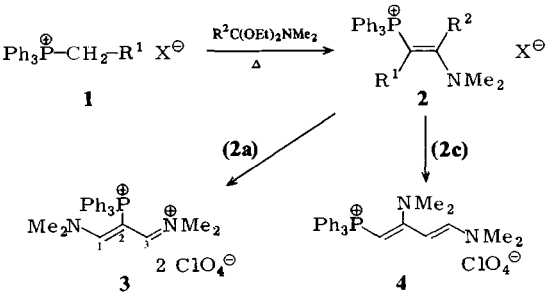
Phosphoniovinamidinium Salts**

By *Rudolf Gompper**, *Eckard Kujath*, and *Hans-Ulrich Wagner*

Dedicated to Professor Hermann Stetter on the occasion of his 65th birthday

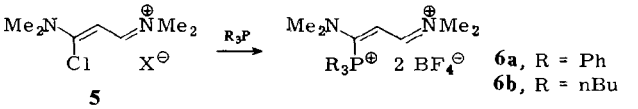
Acceptor moieties in the 1-position of vinamidinium salts increase the positive charge density on C-3 and thus enhance the reactivity of this position towards nucleophiles in accord with the allopolarization principle[1]. Carbonyl groups have been used as acceptors. We have now turned our attention to the scarcely investigated vinamidinium salts bearing cationic substituents; phosphoniovinamidinium salts were hitherto unknown.

Analogously to the preparation of vinamidinium salts from β-aminovinyl ketones, 2-phosphoniovinamidinium salts ought to be accessible from β-dialkylaminovinylphosphonium salts **2**[2]. Surprisingly, they are obtained quite smoothly from the "non-activated" phosphonium salts **1**[3] by heating (≈130 °C) with amide acetals (**2a**, 92%, m.p. 153–156 °C; **2c**, 74%, m.p. 268–269 °C). Reaction of dimethylformamide/phosphoryl chloride/$NaClO_4$ with **2a** at 60–70 °C yields the sought after 2-phosphoniovinamidinium salt **3** (82%, m.p. 233–234 °C, UV/VIS ($CHCl_3$): λ_{max} = 327.5 nm). **2c** does not react at C-1, but at the methyl group to give a 1-phosphoniomethylvinamidinium salt, which can be converted with sodium carbonate into the phosphonium salt **4**.

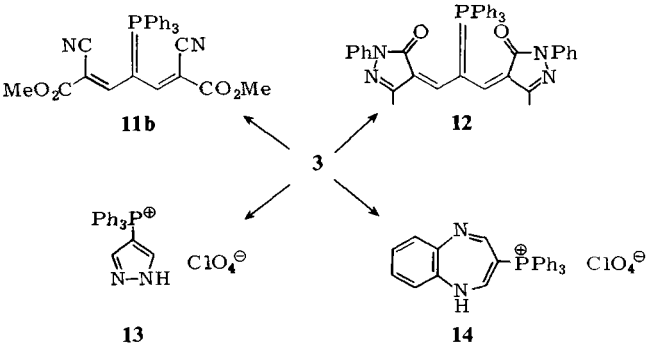


a, $R^1 = R^2 = H$, X = Br; **c**, $R^1 = H$, $R^2 = CH_3$, X = I

The 1-phosphoniovinamidinium salt **6** (**6a**: 31%, m.p. 230–232 °C, $\lambda_{max}(CH_2Cl_2)$ = 375 nm; **6b**: 56%, m.p. 130 °C, λ_{max} = 375 nm (CH_2Cl_2)) is obtained by heating **5** with phosphanes in ethanol in presence of $NaBF_4$. 1-Pyridiniovinamidinium salts are obtainable in a similar way.—It is worth mentioning that **6** absorbs at longer wavelength than **3** in the UV/VIS, while both absorb at longer wavelength than the parent compound (λ_{max} = 312.5 nm). Other acceptor moieties such as 1-ethoxycarbonyl and 1-pyridino (λ_{max} = 327 and 320 nm, resp.) give rise to no such long-wavelength absorption.



The 2-phosphoniovinamidinium salt **3** reacts with numerous nucleophiles. Scheme 1 shows some examples.



Scheme 1 (selection). **3** + methyl cyanoacetate (KOH, MeOH, reflux) → **11b** (90%, m.p. 219–223 °C, $\lambda_{max}(CH_2Cl_2)$ = 438 nm); **3** + methylphenylpyrazolone (NaH, THF, 20 °C) → **12** (32%, m.p. 270–272 °C, $\lambda_{max}(CH_2Cl_2)$ = 510 nm). The compounds **12** exist as internal salts. **3** + hydrazine (in acetonitrile) → **13** (78%, m.p. 240–245 °C); **3** + *o*-phenylenediamine (in acetonitrile, ≈80 °C) → **14** (71%, m.p. >360 °C).

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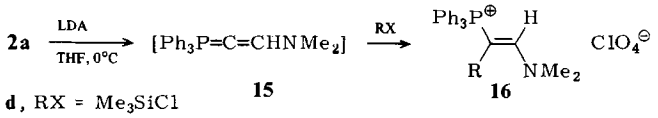
[**] This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie.



2a, which is only a weak nucleophile, can be converted with lithium diisopropylamide into the "phosphaallene ylide" **15** (cf. [4]), which reacts *in situ* with a variety of electrophiles to give compounds **16** (example: **16d**, 78%, m.p. 202–203 °C).

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The complete manuscript of this communication appears in: *Angew. Chem. Suppl. 1982*, 1302–1308

[1] R. Gompper, R. Sobotta, *Angew. Chem. 90* (1978) 808; *Angew. Chem. Int. Ed. Engl. 17* (1978) 760.
[2] E. Schweizer, M. A. Calcagno, *J. Org. Chem. 42* (1977) 2641.
[3] Reactions of **1**, R^1 = aryl, CO_2Me, cf. R. F. Abdulla, R. S. Brinkmeyer, *Tetrahedron 35* (1979) 1675.
[4] H. J. Bestmann, *Angew. Chem. 89* (1977) 361; *Angew. Chem. Int. Ed. Engl. 16* (1977) 349; H. J. Bestmann, K. Roth, *Tetrahedron Lett. 22* (1981) 1681; *Note added in proof* (12. 6. 82): The phosphaallene ylide **15** was first prepared by H. J. Bestmann and G. Schmid (G. Schmid, Dissertation, Universität Erlangen-Nürnberg, 1974; H. J. Bestmann, personal communication).

$Cs_7Fe_4Te_8$, A Compound with $[Fe_4Te_8]$ Clusters

By *Welf Bronger**, *Manfred Kimpel*, and *Dieter Schmitz*

Dedicated to Professor Friedrich Asinger on the occasion of his 75th birthday

The crystal structures of the previously known alkali metal thioferrates and selenoferrates are characterized by edge-linked tetrahedra, whose corners are occupied by chalcogen atoms centered by iron atoms. Hence, compounds of general composition $AFeX_2$ (A = K, Rb, or Cs; X = S or Se) crystallize in chain structures with a $^1_\infty[FeX_{4/2}]$ framework of tetrahedra[1], whereas the sodium compounds Na_3FeX_3 contain isolated $[FeX_2X_{2/2}]_2$ double tetrahedra[2].

We have now prepared the first alkali metal telluroferrate as anthracite colored needles with a metallic luster by allowing a mixture of iron and cesium carbonate to react in a stream of hydrogen charged with tellurium at 1050 K. Its composition is $Cs_7Fe_4Te_8$. The structure was determined from single crystal X-ray data ($Ag_{K\alpha}$ radiation, graphite monochromator; 1595 symmetry-independent reflections with $F_0^2 > 3\sigma(F_0^2)$ in the range $1° < \theta < 30°$; $R = 0.038$).

Isolated $[Fe_4Te_8]$ clusters, in which the iron atoms are tetrahedrally surrounded by tellurium atoms, occur as the characteristic units. The four tetrahedra are mutually linked such that each is joined to the others *via* three edges, corresponding to $[FeTeTe_{3/3}]_4$ (cf. Fig. 1). The $[Fe_4Te_8]$ cluster has approximate T_d symmetry, although only a twofold axis is provided by the space group. Corresponding to this, values for the FeFe distances were found which vary within the threefold standard deviation of the average value 2.847(2) Å. The coordination of the cesium atoms is determined from the atomic arrangement $Cs_7(Fe_4)Te_8$, which corresponds to that in cesium chloride.

The $[Fe_4Te_8]$ cluster represents the first tellurium analog of the active sites of the 4 Fe4S ferredoxins. Of note is that the oxidation number of iron atoms in $Cs_7Fe_4Te_8$ of

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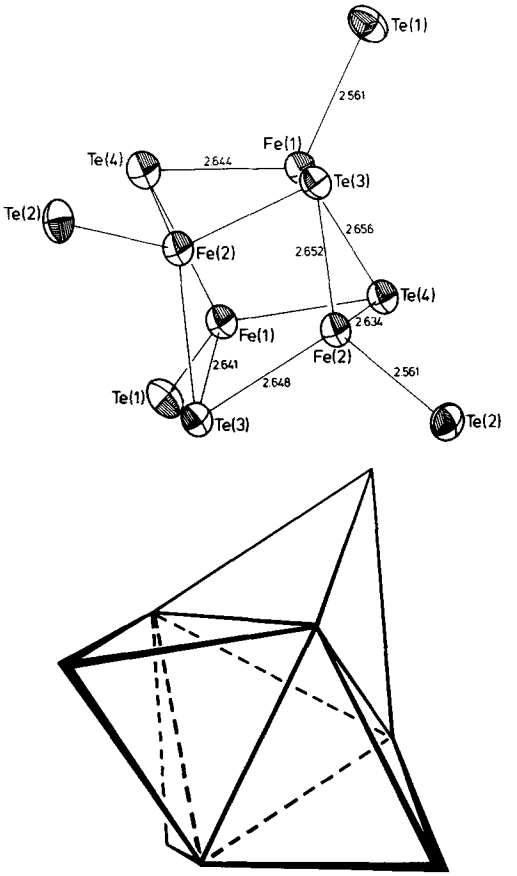

Fig. 1. Top: $[Fe_4Te_8]$ cluster. The standard deviations of the atomic distances are 0.001 Å. — Bottom: linkage of the tetrahedra in the $[Fe_4Te_8]$ cluster.

+ 2.25 is the same as in the reduced form of ferredoxins.

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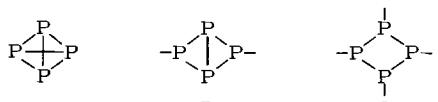
German version: *Angew. Chem. 94* (1982) 562

[1] J. W. Boon, C. H. MacGillary, *Recl. Trav. Chim. Pays-Bas 61* (1942) 910; W. Bronger, *Naturwissenschaften 53* (1966) 525; *Z. Anorg. Allg. Chem. 359* (1968) 225; A. Kyas, Dissertation, Technische Hochschule Aachen 1981; W. Bronger, *Angew. Chem. 93* (1981) 12; *Angew. Chem. Int. Ed. Engl. 20* (1981) 52.
[2] P. Müller, W. Bronger, *Z. Naturforsch. B 34* (1979) 1264; *B 36* (1981) 646.

The First Tetraphosphabicyclobutane**

By *Edgar Niecke**, *Reinhold Rüger*, and *Bernt Krebs*

The previously unknown bicyclobutane analogue **B** of the series of phosphorus homocycles **A**–**C** is of vital importance regarding mechanistic aspects of the reactions of the elemental phosphorus[1].



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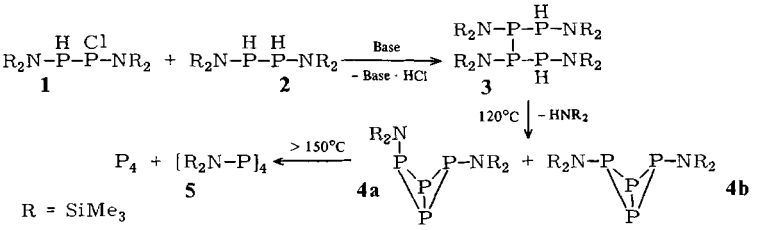
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Starting from the diaminodiphosphanes **1** and **2**[2a] we have now succeeded in synthesizing the tetraphosphabicyclobutane system (**4a**, **b**) by PP-coupling to give the tetraphosphane **3** and subsequent cyclizing amine-elimination.



4a, **b** are pyrophoric, thermally remarkably stable compounds, of which **4b** is obtained in pure form from the isomeric mixture by crystallization. Its composition is confirmed by correct elemental analysis and by the mass spectrum (field ionization, $M^+ = 444.1$).

The $^{31}P\{^1H\}$-NMR spectrum of **4a**, **b** (30% in CD_2Cl_2, H_3PO_4 ext.) shows the resonance absorptions of the bridgehead atoms, as expected, at very high field [$\delta = -222.5$ (**4a**), -287.3 (**4b**)]. The signal pattern for the resonance absorptions of the peripheral phosphorus atoms, shifted about 200 ppm downfield, affords proof of the *cis,trans*-form for **4a** ($\delta = -19.7$, -43.4, $^1J_{PP} = \pm 242$, ± 255 Hz, $^2J_{PP} = \pm 31.5$ Hz) and is consistent with a C_{2v} symmetry[3] for **4b** ($\delta = -79.1$, $^1J_{PP} = 225$ Hz), where model considerations support the sterically favored *trans,trans*-arrangement. This could be confirmed by a complete X-ray structure analysis (Fig. 1).

The P—P bond lengths of the peripheral phosphorus atoms being 2.22—2.23 Å correspond to a "normal" single bond. A surprising feature, however, is the extremely short bridgehead bond, which, with a value of 2.13 Å (P_4: 2.21 Å) indicates considerable double bonding. According to calculations[2b] this "π-bonding" arises from an effective charge transfer of the equatorially arranged bis(trimethylsilyl)amino groups (angle between the normals to the planes Si_2N and NPPN: 92°) to the central P—P bond. Also worthy of note is the transannular P—P distance of only 2.81 Å (bonding angle 95.2°).

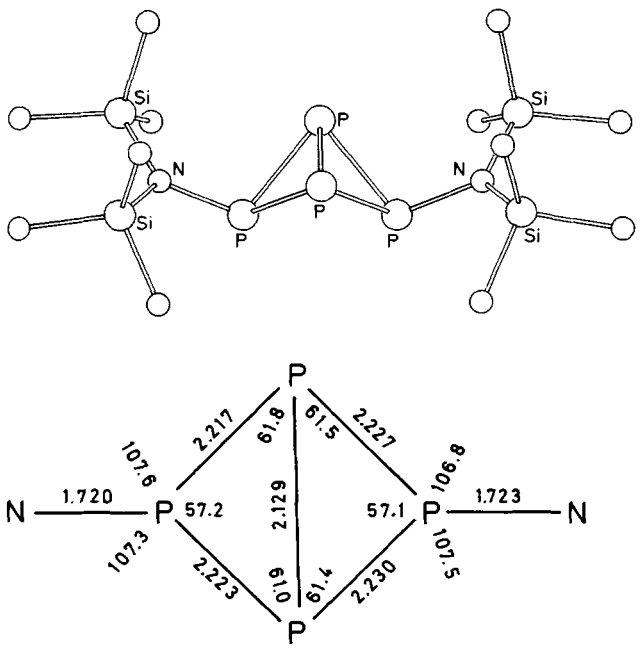


Fig. 1. Top: Molecular structure of **4b** in the crystal; bottom: most important bond lengths and angles ($\sigma < 0.005$ Å and 0.04°, respectively). **4b** crystallizes monoclinically, space group $P2_1/c$, $a = 11.872(2)$, $b = 18.058(3)$, $c = 12.259(2)$ Å, $\beta = 105.34(2)°$, $\rho_x = 1.17$ g cm^{-3}, $Z = 4$ (measured at -115 °C). The crystal structure was determined by direct methods (MULTAN) from 2933 single-crystal diffractometer data and refined to $R = 0.065$.

The instability to be expected for the tetraphosphabicyclobutane system **B** compared to a decomposition into **A** and **C** manifests itself in the fragmentation into phosphorus and **5** above 150 °C[2a].

Procedure

A mixture of **1** (0.005 mol), **2** (0.05 mol) and quinoline (20 mL) was stirred for 24 h at 60 °C/10 torr under an inert gas. Extraction of the reaction mixture with 100 mL of *n*-pentane furnished essentially only **3**[4] and unreacted **2**. After removal of solvent from the extract, vacuum short-path pyrolysis at 130—135 °C/0.5 torr afforded 8 g of the crude product (**4a**, **b**) as a red, highly viscous oil, which still contained *ca.* 5% of **2**, **5** and P_4. **4b** could be isolated in pure form as ebony colored needles (2.5 g ≙ 11%) by recrystallization from a little *n*-pentane.

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[1] C. Brown, R. F. Hudson, G. A. Wartew, *Phosphorus Sulfur* 5 (1978) 67, and references cited therein.
[2] a) E. Niecke, R. Rüger, *Z. Naturforsch.*, in press; b) W. W. Schoeller, C. Lerch, *Inorg. Chem.*, in press.
[3] ^{1}H- and $^{13}C\{^1H\}$-NMR spectra of **4b** are likewise consistent with the C_{2v} symmetry: $\delta^1H = 0.3$; $\delta^{13}C = 4.2$ (q), $|^3J_{PC} + {}^4J_{PC}| = 4.8$ Hz (30% in CD_2Cl_2, TMS int.).
[4] ^{31}P-NMR: $\delta = 76.5$, 7.5, $^1J_{PP} = 215$ Hz (preferred stereoisomer).

Synthesis of Trisubstituted Olefins *via* Trimethylsilylated Phosphorus Ylides

By *Hans Jürgen Bestmann** and *Andreas Bomhard*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

The synthesis of phosphorus ylides **6** with $R^1 \neq R^2$ (R^1, $R^2 \neq H$) causes problems, since the reaction of secondary alkyl halides with triphenylphosphane to afford phosphonium salts also leads to elimination. Secondary reactions afford a mixture of isomeric phosphonium salts, which can only be separated with difficulty. The alkylation of ylides **1** with alkyl halides **5** also produces mixtures[1].

We have found that the pure ylides **6** can be synthesized and immediately converted *via* the following route: reaction of **1** and **2** (molar ratio 2:1) yields, *via* transylidation[1a], the salt **4** and the silylated ylides **3**[2,3], which react with the halogen compounds **5** to afford the phosphonium salts **7**[3]. Desilylation of **7** with cesium fluoride[4] (with tetra-*n*-butylammonium fluoride yields are, in general, poor) results in formation of the disubstituted ylides **6**. Addition of aldehydes **8** (best in dimethylformamide) after the desilylation leads to trisubstituted olefins **9** *via* a Wittig reaction[3].

Wittig reactions with ylides such as **6d** and **6i** (see Table 1), which can hardly be prepared from the corresponding

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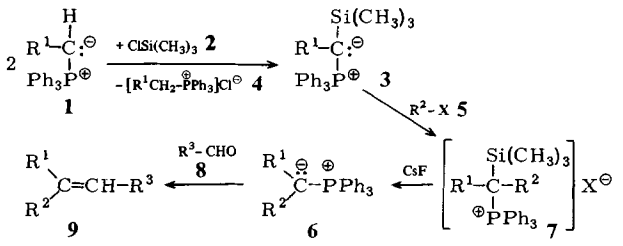

droxy-2-(1,2,4-triazol-1-yl)acrylic acid ester **4** is obtained in good yields. **2** reacts with chlorotrimethylsilane to give the trimethylsilyl enol ether **3**, whose hydrolysis, which already occurs on removal of the sodium chloride formed in presence of moist air, likewise gives **4**, in quantitative yield.

The ^{1}H-NMR spectrum of the ester **4** in $CDCl_3$ and dimethyl sulfoxide (DMSO) shows that only the enols are present. In the case of **4** it was found by ^{1}H-NMR and

Table 1. Synthesized products **7** and **9**.

				7			**9**		
	R^1	R^2	X	Yield [%]	M.p. [°C] (decomp.)	R^3	Yield [%]	B.p. [°C/torr]	E : Z [a]
a	CH_3	CH_3	I	92	188–189	C_6H_5	61	66/12	
b	CH_3	C_2H_5	I	84	198–201	n-C_8H_{17}	46	108–112/16	58 : 42
c	CH_3	CH_2=CH–CH_2	I	94	186–187	n-C_8H_{17}	83	78–81/1.0	53 : 47
d	CH_3	C_6H_5–CH_2	I	96	200–202	C_6H_5	45	90/0.05	11 : 89
e	CH_3	Br	Br	[b]		C_6H_5	15	102/12	4 : 96
f	CH_3	I	I	[b]		C_6H_5	35	110/12	1 : 99
g	C_2H_5	CH_3	I	88	198–201	C_9H_{15} [c]	52	70–75/0.6	[d]
h	n-C_4H_9	CH_3	I	93	192–194	$C_{10}H_{19}$ [e]	42	125/1.8	57 : 43
i	H	C_6H_5–CH_2	Br	91	197–199	C_6H_5	55	80/0.05	23 : 77

[a] Determined by gas chromatography. [b] Reacted further without being characterized. [c] $(CH_3)_2C$=CH–$(CH_2)_2$–$C(CH_3)$=CH (**8g** = citral). [d] 4 isomers (22 : 39 : 15 : 24), not unambiguously assigned. [e] CH_2=CH–$(CH_2)_8$.

phosphonium salts because of simultaneous Hofmann degradation, can also be carried out in this way[5a].

Our conceptions of the mechanism of the Wittig reaction[5b] do not lead us to expect high stereoselectivity in the formation of trisubstituted olefins **9** from **6** with substituents R^1 and R^2 having similar steric and electronic structure. This is conformed by the results in Table 1.

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[1] a) H. J. Bestmann, *Angew. Chem. 77* (1965) 609, 651, 850; *Angew. Chem. Int. Ed. Engl. 4* (1965) 583, 645, 830; b) H. J. Bestmann, H. Schulz, *Chem. Ber. 95* (1962) 2921.

[2] The reaction has already been described for R^1 = H, and also the subsequent reaction with methyl iodide: D. Seyferth, G. Singh, *J. Am. Chem. Soc. 87* (1965) 4156; H. Schmidbaur, W. Tronich, *Chem. Ber. 100* (1967) 1032.

[3] **3**: **2** (220 mmol) is added dropwise to a stirred solution of **1** (400 mmol) in 1 L of benzene at room temperature. The mixture is refluxed for 40 h, **4** is filtered off, and the crystalline ylide **3** isolated by removing the solvent.—**7**: **5** (22 mmol) in 50 mL of ether is added dropwise to a stirred solution of **3** (20 mmol) in 100 mL of ether at room temperature. At the end of the reaction (decoloration) the salt **7** is filtered off and dried *in vacuo*.—**9**: A solution of **7** (20 mmol), and **8** (22 mmol) in 100 mL of anhydrous dimethylformamide is treated with CsF (22 mmol) and stirred for 1–2 d at room temperature. After hydrolysis with 150 mL of water, the mixture is extracted with pentane (3 × 50 mL). The extract is chromatographed on silica gel 60 using petroleum ether and subsequently distilled.

[4] For an analogous desilylation of **7**, R^1 = R^2 = H, cf. E. Vedejs, G. R. Martinez, *J. Am. Chem. Soc. 101* (1979) 6452.

[5] a) H. J. Bestmann, H. Häberlein, I. Pils, *Tetrahedron 20* (1964) 2079; b) H. J. Bestmann, *Pure Appl. Chem. 52* (1980) 771.

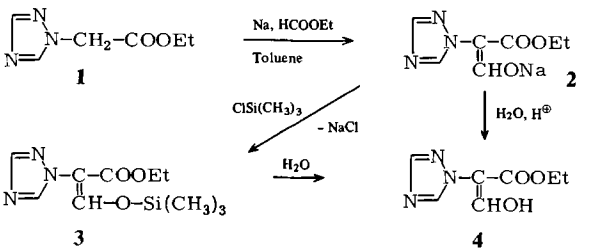
3-Hydroxy-2-(1,2,4-triazol-1-yl)acrylic Acid Ethyl Ester and *O*-Functional Derivatives

By *Thomas Maier** and *Friedrich Cavagna*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

The triazolylacetic ester **1** can be formylated with ethyl formate[1]. On acidifying the sodium enolate **2**, the 3-hydroxy-2-(1,2,4-triazol-1-yl)acrylic acid ester **4** is obtained in good yields. **2** reacts with chlorotrimethylsilane to give the trimethylsilyl enol ether **3**, whose hydrolysis, which already occurs on removal of the sodium chloride formed in presence of moist air, likewise gives **4**, in quantitative yield.

The ^{1}H-NMR spectrum of the ester **4** in $CDCl_3$ and dimethyl sulfoxide (DMSO) shows that only the enols are present. In the case of **4** it was found by ^{1}H-NMR and ^{13}C-NMR spectroscopic investigations that only the *Z*-form exists in DMSO, whereas both the *Z*- (*ca.* 88%)



and the *E*-form (*ca.* 12%) are present in $CDCl_3$ [^3J(H, CO_{trans}) = 8 Hz, *E*-form; ^3J(H, CO_{cis}) = 2 Hz, *Z*-form]. In $CDCl_3$ the OH protons of the *Z*-form form hydrogen bonds with N2 of the triazole moiety, and those of the *E*-form form such bonds with the oxygen of the carbonyl group.

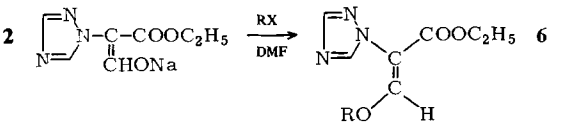
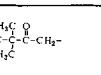
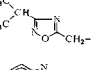
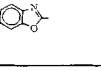


Table 1. Synthesized compounds **6** (selection).

R	M.p. [°C]	R	M.p. [°C]
H	157–159		94–96
$C_6H_5CH_2$	79–82		74–75
p-Cl-$C_6H_4CH_2$	100–102		oil
m-C_6H_5-O-$C_6H_4CH_2$	oil		133–135

Alkylation and acylation of the enolates **2** in dimethylformamide (DMF) take place only at the oxygen under the

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conditions chosen (Table 1)[2]; the products **6** are always *Z*-configurated.

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The complete manuscript of this communication appears in:
Angew. Chem. Suppl. 1982, 1246–1254

[1] a) Review on the formylation of methylene groups: J. Mathieu, J. Weill-Raynal: *Formation of C—C Bonds, Vol. I, Introduction of a Functional Carbon Atom*, Thieme, Stuttgart 1973, p. 176; b) **2**: A mixture of ethyl formate (144.3 g, 1.95 mol), ethanol (38.3 g, 0.83 mol), and **1** (201.5 g, 1.3 mol) is added dropwise within 15 min to a suspension of sodium (31.05 g, 1.35 mol) in toluene. The mixture is briefly warmed to 30 °C, whereupon an exothermic reaction sets in. The internal temperature remains at 31 °C for 2 h, and solid separates out. After 12 h a thick, yellowish mass has formed. The mixture is then stirred for a further 6 h at 60–70 °C, cooled, the solvent removed by suction, and the residue washed with diisopropyl ether. After drying, 262.5 g (98.5%) of **2** (m.p. 232–235 °C) is obtained.

[2] General procedure for **6**: A solution of **2** (0.1 mol) in DMF (*ca.* 50 mL) is treated dropwise within *ca.* 5 min with 0.1 mol of the halogen compound (in the case of solids with a concentrated solution of the halogen compound in DMF). The mixture is stirred for 60 min at room temperature (in the case of an exothermic reaction the mixture is allowed to warm and then cooled to room temperature again) and 90 min at 60–70 °C. After cooling, the sodium halide is removed by suction and the DMF solution is evaporated to dryness in a vacuum and treated with acetone; undissolved sodium halide is removed by suction and the acetone is distilled off from the filtrate. The crude products are, in the case of solids, washed with diisopropyl ether and water, in the case of oils they are treated with H_2O/chloroform (1:1); the product is isolated from the chloroform phase.

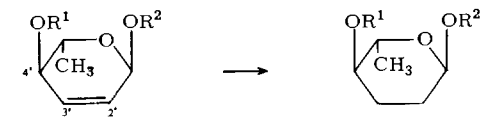
Synthesis of Cardenolide 3β-2′,3′-Dideoxy-α,L-rhamnopyranosides**

By *Ulrich Stache**, *Kurt Radscheit*, *Werner Haede*, and *Werner Fritsch*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

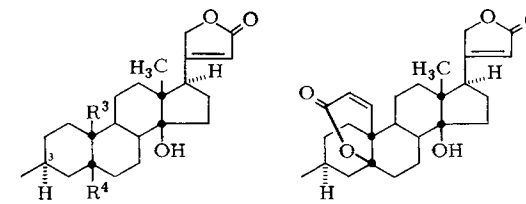
We had previously synthesized a series of 3β-(2′,3′-didehydro-2′,3′-dideoxy-α-L-rhamnopyranosyloxy)-cardenolides with positive inotropic activity[2a] from 3,4-di-*O*-acetyl-1,2,6-trideoxy-L-arabino-1-hexenopyranose (diacetyl-L-rhamnal) and cardenolide aglycons, *e.g.* 3β,14-dihydroxy-5β,14β-card-20(22)-enolide (digitoxigenin) according to the "glycal method" of *Ferrier et al.*[1]; owing to the 2′,3′-double bond in the sugar moiety they already hydrolyze at pH 5, and thus are unsuitable as cardiac glycosides. Hydrogenation of the 2′,3′-double bond should confer a better acid-stability on the glycosidic coupling.

During the catalytic hydrogenation of **1a**[2a]—Pd/$CaCO_3$ (10%), C_2H_5OH, 760 torr, 20 °C; 92% yield after filtering off the catalyst, evaporation to dryness, and recrystallization from ethanol—the 2′,3′-double bond in the glycoside moiety is reduced regioselectively. As proven by the UV spectrum [(C_2H_5OH) $\lambda_{max}=217$ nm, $\varepsilon=15800$], IR spectrum [(KBr) $\nu=1775$, 1735 cm^{-1}], mass spectrum [$m/z=530$, M^+], and ^{1}H-NMR spectrum [($CDCl_3$) $\delta=5.9$ (t, 22-H), 4.9 (AB system, 21-H_2)] of the resulting **2a** [m.p. = 229 °C; $[\alpha]_D^{20}=-54$ ($HCCl_3$, $c=0.5$)], the 20(22)-double bond of the butenolide ring is not attacked. Mild hydrolysis of the 4′-acetate group of **2a**—$KHCO_3$ in methanol/water (11:1), 25 min reflux—affords 3β-(2′,3′-dideoxy-α-L-rhamnopyranosyloxy)digitoxigenin **2b**[5] in 80% yield [m.p. 218 °C; $[\alpha]_D^{20}=-41$ (CH_3OH, $c=0.5$)]. In diverse animal experiments[3], **2b** proved to be three times more active than digoxin with respect to the inotropic action, for almost quantitative oral resorption; it has a duration of effect like the non-orally active k-strophanthin as well as a therapeutically acceptable acid-stability (stable at 20 °C in ethanolic solution up to *ca.* pH 1). **2b** could find use as an "oral strophanthin"[3]. In analogy to the reaction sequence **1a**→**2a**→**2b** the 3β-2′,3′-dideoxy-α-L-rhamnopyranosides of the k-strophanthidin, **3b** [m.p. 226–228 °C; UV (CH_3OH): $\lambda_{max}=217$ nm, $\varepsilon=15800$; $[\alpha]_D^{20}=-14.2$ (CH_3OH, $c=0.5$)], and of the 5,19-(epoxycarbonylmethyleno)digitoxigenin, **4b**[2a] [m.p. 184–186 °C; UV (CH_3OH): $\lambda_{max}=214$ nm, $\varepsilon=22300$; $[\alpha]_D^{20}=-28.0$ (CH_3OH, $c=0.5$)], can also be obtained.



1a, R^1 = $COCH_3$, R^2 = X
1b, R^1 = H, R^2 = X

2a, R^1 = $COCH_3$, R^2 = X
2b, R^1 = H, R^2 = X
3a, R^1 = $COCH_3$, R^2 = Y
3b, R^1 = H, R^2 = Y
4a, R^1 = $COCH_3$, R^2 = Z
4b, R^1 = H, R^2 = Z



X, R^3 = CH_3, R^4 = H
Y, R^3 = CHO, R^4 = OH

Z

We have already previously reported[2b,4] on other regioselective additions to the 2′,3′-double bond of **1a**.

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[**] Preparation of Unsaturated Lactones of the Steroid Series, Part 13.—Part 12: U. Stache, K. Radscheit, W. Haede, W. Fritsch, *Liebigs Ann. Chem. 1982*, 342.

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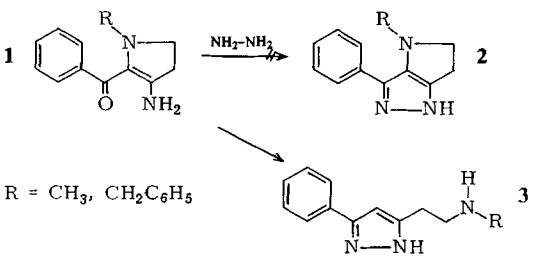
Anomalous Reaction of Hydrazine with β-Aminovinyl Ketones

By *Rudolf Kunstmann** and *Erich F. Paulus*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

There are numerous examples of the synthesis of pyrazoles from β-aminovinyl ketones or 1,3-dicarbonyl compounds and hydrazine or hydrazine derivatives[1]. It was therefore unexpected that 3-amino-2-benzoyl-3,4-dihydropyrroles **1** do not give the desired 1,4,5,6-tetrahydropyrrolo[3,2-*c*]pyrazoles **2**, but 5-(2-aminoethyl)-3-phenyl-1*H*-pyrazoles **3** on reaction with excess hydrazine.



The potential structural isomers of **3** could not be distinguished from one another by ^{1}H-NMR and mass spectroscopy. X-ray crystal structure analysis of **3**, R = $CH_2C_6H_5$, confirmed the proposed structure.

The balance of the reaction of **1** with hydrazine indicates that a reduction step is involved in the formation of **3**; in the course of the reaction 1/2 mol nitrogen per mol of **1** is eliminated. It has not yet been established whether the intermediate **2** is formed.

Procedure

A mixture of hydrazine hydrate (2 mL), ethanol (15 mL), and **1**, R = $CH_2C_6H_5$ (2.78 g, 10 mmol) is heated for 2 h under reflux. The resulting solution is diluted with water, extracted with ethyl acetate, and the organic phase dried and concentrated. The residual oil is crystallized from isopropyl alcohol and subsequently converted into the hydrochloride; yield 1.9 g (63%) **3**·HCl, R = $CH_2C_6H_5$, m.p. = 213–215 °C. In an analogous manner **3**, R = CH_3, was obtained as the dioxolate in 52% yield; m.p. = 187 °C.

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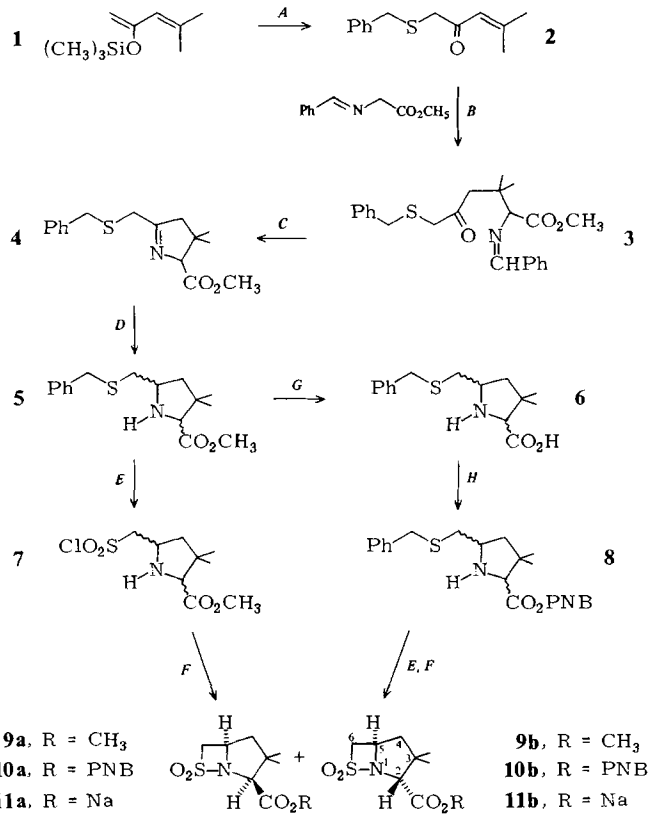
Synthesis of Bicyclic β-Sultams

By *Friedrich Cavagna, Wolfgang Koller**, *Adolf Linkies, Herbert Rehling*, and *Dieter Reuschling*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

It is generally assumed that the biological activity of β-lactam antibiotics depends on the reactivity of the β-lactam ring. Substitution of the CO group of the β-lactam by an SO_2 group leads to the more reactive β-sultams. We report here on the synthesis of bicyclic β-sultams (Scheme 1), whose structure resembles that of the penicillins.



Scheme 1. PNB = *p*-nitrobenzyl. *A:* 1. Br_2, CH_2Cl_2, −65 °C; 2. $PhCH_2SH$, Et_3N, CH_2Cl_2, RT.—*B:* KOH, tetrahydrofuran, Bu_4NBr, RT, 20 h.—*C:* 1. 2N HCl; 2. K_2CO_3.—*D:* $NaBH_3CN$, MeOH, citric acid, CH_2Cl_2.—*E:* Cl_2, CH_2Cl_2, EtOH, 10 °C.—*F:* Et_3N, CH_2Cl_2, 0 °C.—*G:* KOH, MeOH, H_2O, 18 h.—*H:* *p*-$NO_2C_6H_4OH$, $CHCl_3$, *p*-$CH_3C_6H_4SO_3H$, 30 h.

Mesityl oxide is converted by regioselective bromination of the silylenol ether **1**[2] and subsequent reaction with benzylthiol into the benzylthiomesityl oxide **2**, which on reaction with the *N*-benzylidene derivative of glycine methyl ester[3] forms the adduct **3**; this can be cleaved by treatment with 2N hydrochloric acid into the amine and benzaldehyde. After extraction of the aldehyde from the acidic solution, addition of K_2CO_3 leads to spontaneous cyclization of the amine to give the pyrroline **4**, which is reduced to the pyrrolidine **5** with $NaBH_3CN$. Both possible diastereomers are formed in a ratio of 4:1. Oxidation of **5** with chlorine in the presence of ethanol affords the sulfonic acid chloride **7** and benzyl chloride; **7** is converted without purification into the non-hydrolyzable β-sultam ester **9**. The *p*-nitrobenzyl ester **10** cannot be prepared in this way, since the benzylidene derivative of glycine *p*-nitrobenzyl ester does not react with **2**. However, the pyrrolidine **5** can be hydrolyzed to **6**, and then reesterified with *p*-nitrobenzyl alcohol to **8**. As expected, the reactions of **8** lead to a mixture of the diastereomers **10**, which can be separated by column chromatography. Finally, catalytic hydrogenation of **10a** and **10b** affords the sodium salts **11a** and **11b**, respectively. The sodium salt **11b**—like the analogous β-lactam penicillanic acid[4] too—is devoid of any significant antibacterial activity.

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The stereochemistry of the diastereomers **9**—**11** was determined ^{1}H-NMR spectroscopically, in particular by comparison with analogous β-lactams[5]. In the case of **9b**, unequivocal assignment of the relative configuration of the protons in the 2-position and 5-position was possible by means of FT-NOE (nuclear Overhauser effect) difference spectroscopy: saturation of the protons of the methyl group at $\delta = 1.05$ and at $\delta = 1.45$ led to a marked nuclear Overhauser effect at H-5 and H-2, respectively.

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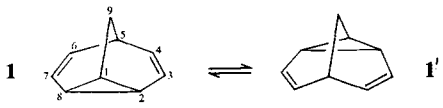
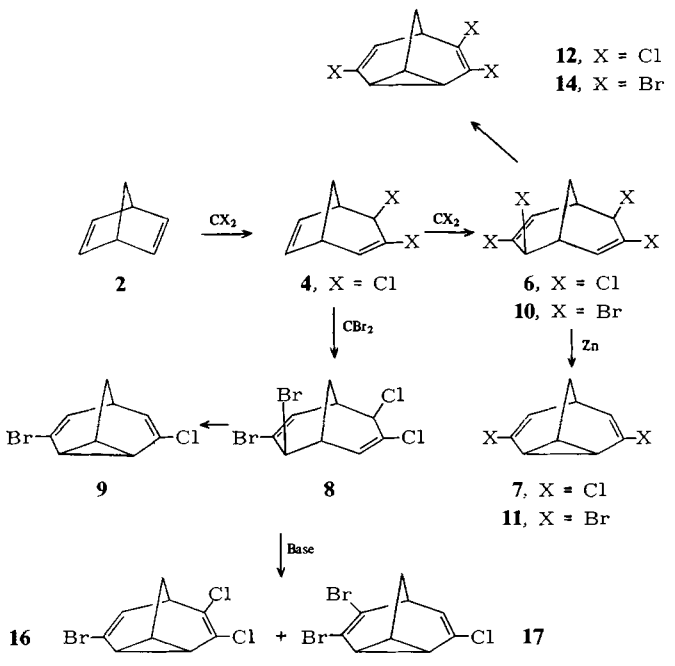
A Simple Synthesis of Di- and Trihalobarbaralanes

By *Charles W. Jefford*, Jean-Claude Rossier,* and *Jacques A. Zuber*

Fluxional molecules such as barbaralane **1** ⇌ **1'** are not easily accessible[3]. We now present a short synthesis of di- and trihalobarbaralanes (**7**, **9**, **11** and **12**, **14**, **16**, **17**, respectively) from norbornadiene **2**.



When excess dichlorocarbene, generated by the phase transfer method[4], is allowed to react with **2** several products are obtained. The product of interest **6** is formed as a result of double addition. It is easily separable from the product mixture, but can also be conveniently obtained stepwise from **4**. Compound **6** possesses two *exo*-Cl atoms which are easily removed by zinc dust to give 3,7-dichlorobarbaralane **7**. By analogy, addition of dibromocarbene[7] to **4** gives **9** *via* **8**. Double addition of dibromocarbene to **2** gives, among others, the expected tetrabromo derivative **10**, which (analogously to **6**→**7**) can be converted into **11**. The NMR spectra of all three 3,7-dihalobarbaralanes **7**, **9**, and **11** at room temperature show them to be fully fluxional molecules just like the parent molecule **1** [*e.g.* **7**: 100.1 MHz ^{1}H-NMR ($CDCl_3$): $\delta = 1.14$ (t, 2 H-9), 2.54 (H-1,5), 4.16 (H-2,4,6,8)].



The trihalo derivatives are also easily prepared from **2** *via* **6**, **8**, and **10**. Dehydrohalogenation of **6** and **10** with base gives **12** and **14**, respectively. However, the action of base on **8** gives a mixture of **16** and **17**.

Unlike **7**, **9**, and **11** all the trihalo derivatives are either nonfluxional or strongly weighted in favor of the structures indicated at room temperature [*e.g.* **12**: $\delta = 1.26$ (H-9m (points towards C-7)), 1.48 (H-9d), 2.22 (H-1), 2.45 (H-8), 2.61 (H-2), 3.13 (H-5), 5.95 (H-6)]. The synthetic procedure described may offer a good route to homoaromatic barbaralanes[9].

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2, 121-46-0; **4**, 35501-78-1; **6**, 82093-51-4; **7**, 82093-52-5; **8**, 82093-53-6; **9**, 82093-54-7; **10**, 82093-55-8; **11**, 82093-56-9; **12**, 82093-57-0; **14**, 82093-58-1; **16**, 82093-59-2; **17**, 82093-60-5.

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Redox Reactions of a Ferrio-arsane and -stibane with Chlorophosphanes: Synthesis of a Diferrioarsonium Chloride and a Stiborane with Asymmetric Iron Atoms[1]

By *Wolfgang Malisch*, Hans-Achim Kaul, Elisabeth Gross,* and *Ulf Thewalt*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

In ferrio-arsane and -stibane $Cp(CO)(Me_3P)Fe—EMe_2$ (E = As, Sb) the trivalent arsenic and antimony atom, re-

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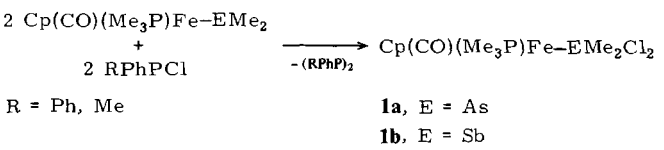
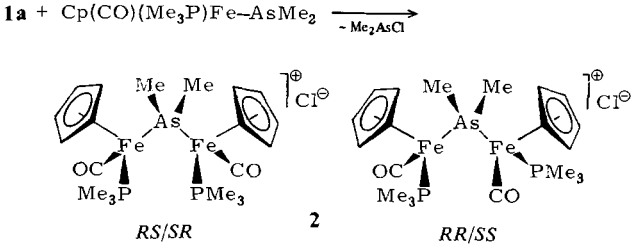
[+] X-ray structure analysis.

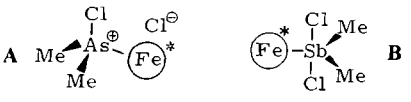
spectively, exhibit pronounced Lewis basicity; thus the compounds can be quaternized with alkyl halides, whereupon salts containing the chiral cations $[Cp(CO)(Me_3P)Fe—EMe_2R]^{\oplus}$ are formed[2]. As has now been found, their reaction with the chlorophosphanes Ph_2PCl and PhMePCl proceeds quite differently: The arsane or stibane is oxidized to a dichloroarsenic(v) or dichloroantimony(v) species, namely **1a** or **1b**; simultaneously the chlorophosphanes are converted into the diphosphanes $(RPhP)_2$.



1b is stable under normal conditions, whereas **1a** is a short-lived intermediate which immediately reacts further *via* $Me_2AsCl/Cp(CO)(Me_3P)Fe—AsMe_2$-exchange to give the diferrio-arsonium salt **2**. Compound **2** has two identical chiral centers and is therefore obtained as the *meso*-form (*RS/SR*) and a diastereomerically related pair of enantiomers (*SS/RR*), which are distinguishable by NMR spectroscopy.



The instability of **1a** can be explained in terms of the ionic arsonium structure **A**[5]. **1b**, which is barely air-sensitive, moderately soluble in benzene, very soluble in nitromethane, and dissolves without decomposition, has a covalent structure—as is reflected in its low conductivity. Thus, **1b** is the first transition metal derivative of pentavalent antimony, which, in addition, for the first time bears three different substituents.



The X-ray structure analysis of **1b** (Fig. 1) shows two independent molecules with almost identical conformation. In accordance with the polarity rule[7], the chiral ferrio group and the two methyl groups assume the equatorial positions, the electronegative chloro-atoms the axial positions at the trigonal-bipyramidally configurated Sb atom. Whereas the SbC bond lengths in **1b** agree quite well with those in known Sb^V compounds, the SbCl bond lengths are distinctly longer [Me_3SbCl_2[10]: 2.13 (Sb—C) and 2.49 Å (Sb—Cl), respectively]. The bulkiness of the $Cp(CO)(Me_3P)Fe$ group implies a wide opening of the FeSbCl angle and a closing of the H_3CSbCH_3 angle compared to the ideal values of 90 and 120°, respectively.

1b represents the first confirmed example of a simply constructed transition metal substituted 5B-element compound with coordination number 5. An analogous structure had already previously been proposed on the basis of spectroscopic findings for the stiboranes $Cp(CO)_3M—SbMe_2Br_2$ (M = Mo, W)[17]. Since the diastereotopic methyl groups in **1b** give only one ^{1}H-NMR signal it is uncertain whether the structure **B** is also preferred in solution. According to previous experiences a rapid inversion of configuration at the metal is not responsible for this NMR finding; it can only be explained in terms of a rapid pseudorotation process at the antimony or a coincidental NMR equivalence of the methyl groups.

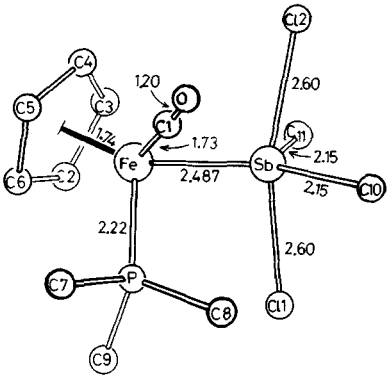


Fig. 1. Molecular structure of **1b** in the crystal. The bond lengths (Å) are the mean values for two crystallographically independent molecules.

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Support Effects on the Growth, Stabilization, and Agglomeration of Low Nuclearity Transition Metal Clusters Synthesized from Metal Atoms Vaporized into Liquid Aryl-Substituted Polymers**

By *Geoffrey A. Ozin** and *Mark P. Andrews*

In this study, we report the effect of liquid aryl-substituted polymers on the growth, stabilization, and agglomeration behavior of arene transition-metal cluster complexes of catalytic interest[1]. Only species of the type $(arene)_mM_n$ (m = 2, n = 1, 2) are formed when atomic metal vapors of groups 4A to 6A are cocondensed with arenes under various conditions[2-4]. Complexes containing up to three metal atoms can be stabilized in liquid α,ω-diphenyloligo(ethylene oxides) containing from five to eleven ether oxygen atoms. In the presence of liquid poly(methylphenyl-

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co-dimethylsiloxane) (DC 510) the cluster size (n = 4, 5), the rate of cluster formation, and stabilization are substantially enhanced. For example, when vanadium atoms are cocondensed with benzene or toluene (matrix, 12—77 K) two species are formed: $(arene)_2V$ showing a metal-ligand charge transfer (MLCT) absorption at $\lambda = 323$ nm, and $(arene)_2V_2$ absorbing at 455 nm. Homo- and heterodimetallic compounds can be produced by direct addition of a transition metal atom to bis(arene)metal (n = 1) sandwich complexes[5] in solution.

Deposition of atomic Mo into liquid α,ω-diphenyloligo(ethylene oxides) at 275—290 K gives rise to mono-, di-, and trimetal compounds ($\lambda_{max} = 318$, 415, and 502 nm, respectively). Clusters having nuclearity $n > 3$ cannot be prepared in these reaction media. Reaction of Mo with DC510 (250 K) gives rise to two additional species: a tetra- and a pentanuclear cluster ($\lambda_{max} = 578$ and 640 nm, respectively). However, only $(arene)_2Mo_2$ is produced when $(arene)_2Mo$ dissolved in phenyl-free, liquid poly(dimethylsiloxane) DC200 is titrated with Mo atoms. Stable, low nuclearity clusters could not be grown in the absence of free arene or arene functionalities in liquid media.

Kinetic analysis of the growth curves for Mo_n in DC510 appears to confirm a stepwise aggregation model. Further studies (viscometry, NMR, ESR) on the DC510/M system indicate (among other factors) the role played by inter- and intramolecular crosslinking *via* $(arene)_2Mo$ complex formation in stabilizing tetranuclear and higher metal clusters: for $(arene)_mM_n$ this decreases from n = 2 to n = 5. Loss of the binuclear $(arene)_2Mo_2$ species supported on DC510, through diffusion-controlled aggregation follows second order kinetics, the rate and activation energy of diffusion being functions of metal loading (variation in crosslink density). Thus the activation energy for the dimerization of $(arene)_2Mo_2$ supported on DC510 (290 K) at low metal loading levels is 4.2 kcal/mol compared to a high loading value of 14.2 kcal/mol: the respective diffusion coefficients of 32.6×10^{-16} and 18.7×10^{-16} cm^2/s reflect the microscopic mobility of the polymer support, which is constrained by increasing crosslinking.

These data together with results of ESR, EXAFS, SIMS, and Raman spectroscopic studies collectively indicate that the growth/agglomeration characteristics in the polymer are determined by a number of effects: 1) the presence or absence of covalently bound arene groups; 2) changes in the microenvironment in the vicinity of the metal aggregate, where cluster size and stability are seen as determined, in part, by the dimensions and arene density of "solvating" cavities. 3) Steric interaction between the immobilized metal aggregate, the polymer support, and the diffusant (metal atom, covalently bound arene, or nucleation site); diffusional encounters are controlled by polymer microdynamics which are dependent both on temperature and crosslink-density. 4) Diffusional limitations which affect the rate of penetration of metal atoms into the polymer (to contribute to cluster growth or be "removed" by a colloid sink), cluster aggregation is also diffusion controlled. 5) Structural changes or constraints imposed on metal aggregates or polymer as a result of binding or stabilization of macromolecules by crosslinking; such changes will control both the number and size distribution of clusters, determining a maximum metal loading limit beyond which colloid formation becomes the favored process for metal atom consumption.

The bis(arene)metal complexes are viewed as "crosslinking" and/or chain propagating agents, as well as metal nucleation sites for the production of clusters. The aggregates are, in part, "solvated" by the ether oxygen atoms of the oligomer or polymer backbone. Evidence suggests that this interpretation is more likely than the alternative involving crown ether or cryptand-like ligand-M_n interactions, without participation of the phenyl substituents.

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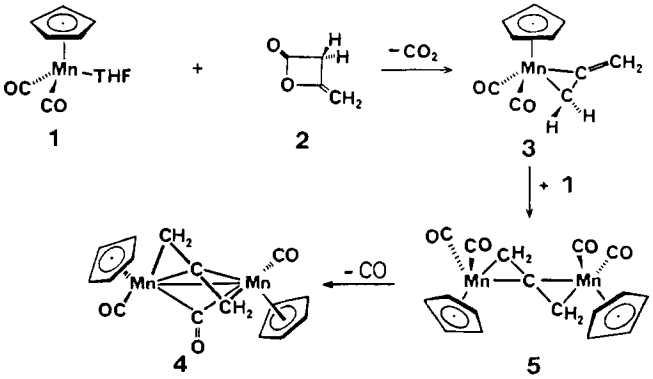
Metal-Induced Decarboxylation of Diketene—A Novel Route to Allene Complexes[1]

By *Wolfgang A. Herrmann**, *Josef Weichmann*, *Manfred L. Ziegler*, and *Heike Pfisterer*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

The synthetic potential of the readily accessible and industrially important[2] diketene **2** has so far been overlooked in organometallic chemistry. We report here on the metal-induced decarboxylation of this compound, which reaction enables the facile and convenient synthesis of allene complexes.

Whereas breakdown of the diketene skeleton requires temperatures around 550 °C and yields besides ketene only traces of allene[2], its decarboxylation takes place under surprisingly mild conditions in the presence of carbonylmetal compounds that are labile towards ligand substitution; concomitantly, allene is incorporated into the organometal substrate. Thus, reaction of the tetrahydrofuran complex **1** with excess diketene **2** in the temperature range −30 to +25 °C leads cleanly, under vigorous evolution of CO_2, primarily to the mononuclear η^2-allene complex **3** (characterized by total elemental analysis, and by IR, ^1H-



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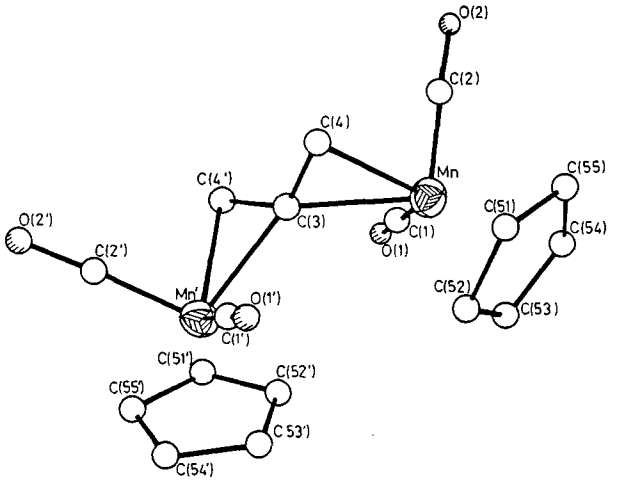

Fig. 1. Structure of the $\mu(\eta^2:\eta^2)$-allene complex **5** in the crystal. $R_w = 0.029$. The angle between the plane of the V-shaped allene bridge and the Mn—Mn vector is 48.6°. The $\eta^2:\eta^2$-coordination rules out a metal-metal bonding with the present stoichiometry on electronic grounds; as expected the Mn—Mn distance is greater than 380 pm.

Table 2 (selected data). Some important bond lengths [pm] and angles [°] in **5**.

MnC(1) 177.8(6), MnC(2) 175.9(6), MnC(3) 214.6(3), MnC(4) 211.9(6), C(3)C(4) 140.8(7), C(1)O(1) 116.2(7), C(2)O(2) 117.1(8); C(4)C(3)C(4') 129.5(0.8), C(1)MnC(2) 87.1(0.3), MnC(4)C(3) 71.8(0.3), MnC(3)Mn' 131.3(0.4)

NMR and mass spectra). The η^2-allene ligand does not fluctuate with respect to the metal-ligand bond [^{1}H-NMR (270 MHz, [D$_8$]THF, 25 °C): $\delta CH_2 = 6.19$ (1 H), 5.66 (1 H), 2.53 (2 H); $\delta C_5H_5 = 4.68$ (5 H)]. Besides **3**, the dinuclear derivatives **4** (< 3%, already known[7]) and **5** (< 10%) with symmetrically bonded V-shaped $\eta^2:\eta^2$-allene bridges (Fig. 1, Table 2) are formed.

The high-yield secondary complexation of the free C=C bond of **3** to the $(\eta^5\text{-}C_5H_5)Mn(CO)_2$ fragment with clean subsequent decarbonylation (**1**+**3**→**5**; **5**→**4**+CO) can be used in general for the straightforward synthesis of previously rarely encountered dinuclear complexes with allene bridges[7-9, 12].

As a test-case, the reaction of diketene **2** with $Fe_2(CO)_9$ may be cited here. Analogously to **3** and **5**[9], the complex $Fe_2(CO)_7(C_3H_4)$ with an $\eta^1:\eta^3$-allene bridge is formed almost quantitatively already at 25 °C; this particular compound was hitherto accessible only by reaction of allene and $Fe_2(CO)_9$ at elevated temperatures (50 °C) and pressures[8]. Our synthetic route to bridged allene complexes also opens up the possibility of synthesizing derivatives containing different metal centers.

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1, 12093-26-4; **2**, 674-82-8; **3**, 82168-19-2; **4**, 73002-71-8; **5**, 82150-25-2.

[1] Complex Chemistry of Reactive Organic Compounds, Part 40. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie (Promotionsstipendium (J. W.)).—Part 39: W. A. Herrmann, J. Weichmann, B. Balbach, M. L. Ziegler, *J. Organomet. Chem. 231* (1982) C69.

[2] D. Borrmann in Houben-Weyl-Müller: *Methoden der Organischen Chemie*, Band VII/4, p. 226 ff., Thieme, Stuttgart 1968.

[7] X-ray structure analysis of **4**: L. N. Lewis, J. C. Huffman, K. G. Caulton, *J. Am. Chem. Soc. 102* (1980) 403; *Inorg. Chem. 19* (1980) 1246.—According to this work compound **4** is formed in unspecified yield by means of H^-/CH_3^+-addition upon the vinylidene precursor $(\mu\text{-}C{=}CH_2)[(\eta^5\text{-}C_5H_5)Mn(CO)_2]_2$.

[8] R. Ben-Shoshan, R. Pettit, *Chem. Commun. 1968*, 247; cf. R. E. Davis, *ibid. 1968*, 248.

[9] Unsuccessful attempts to synthesize manganese-allene complexes (*e.g.* **3**) from free allene: cf. A. Nakamura, *Bull. Chem. Soc. Jpn. 39* (1966) 543.

[12] A. Kühn, C. Burschka, H. Werner, *Organometallics 1* (1982) 496, and references cited therein.

BOOK REVIEWS

An Introduction to Chemical Equilibrium and Kinetics. By *L. Meites*. Pergamon Press, Oxford 1981, xiii, 549 pp., price £ 8.95.

This book was written to serve the new type of beginners' chemistry course at Clarkson College of Technology. The course comprises a first semester of lectures on structure and bonding, and a second semester of lectures based on the present book, both running in parallel with a one-year "integrated" practical course. The book is divided into the following chapters: Chemical Thermodynamics and Equilibrium, Chemical Kinetics, Non-electrolyte Equilibria, Solubility of Ionic Compounds, Acid-base Equilibria, Complex Reactions, Redox Processes, Analytical Chemistry and Stoichiometry, Precipitation, Titration Curves, Errors in Measurement, Activities and Activity Coefficients, Potentiometry, and Spectroscopy. Thus, almost nothing has been left out from the field embraced by classical chemistry.

As a physical chemist I found myself fluctuating between laughter and tears while reading this book. The laughter was a reminder of my own student days, when I heard a world-famous organic chemist announce to his students that "a real chemist has little use for physical chemistry". The tears were provoked by the way this book treats the fundamentals of physical chemistry as "black box" concepts. Thermodynamics are dealt with in 23 pages, and free energy occupies a page or two. Students of chemistry are already reluctant to interrupt chemistry practicals to attend lectures on physical chemistry, and were they to take Mr. *Meites'* book seriously, this trend could not but be reinforced. It is inconceivable to me that a course of study written in this superficial style can possibly produce scientifically creative chemists. No doubt the book can be explained in terms of the widely differing standards encountered in colleges in the United States, not all of which aim to foster a new generation of researchers. The book can be recommended: for physical chemists in search of illustrative examples; for teachers of advanced inorganic or organic chemistry who wish to bridge over into physical chemistry; for undergraduate students who

wish to relate the contents of lectures in physical chemistry to other branches of chemistry.

However, the book cannot be recommended for beginners. To avoid presenting beginners' lectures in this style, the course of study would have to be redesigned to put the physical-chemistry content at the start. However, this presupposes considerable mathematical knowledge, which would have to be acquired at school level and/or in introductory pre-semester courses. — The book should stimulate us all to give careful thoughts to new ways of educating our future chemists.

W. A. P. Luck [NB 557 IE]

Ullmanns Encyklopädie der technischen Chemie. Edited by *E. Bartholomé, E. Biekert, H. Hellmann, H. Ley †, W. M. Weigert †*, and *E. Weise*. Verlag Chemie, Weinheim 1981. 4th edition, Vol. 6: Umweltschutz und Arbeitssicherheit [Environmental Protection and Works Safety]. Volume editor: *E. Weise*. xvi, 830 pp., bound, DM 640.00.—Vol. 20: Radionuklide bis Schutzgase [Radionuclides to Protective Gases], xvi, 705 pp., bound, DM 525.00.

With the appearance of these two volumes the 4th edition of Ullmann has come appreciably closer to completion: all the volumes of the general part are now available and of the alphabetical part only four volumes are still lacking[*].

Volume 6 covers two areas in which considerable changes have taken place in the last ten years. Whereas these areas have always been of great importance to industrial chemists, the newly developed public sensitivity to questions of ecology and safety have led to the situation that the government has become increasingly involved in this field by means of laws and decrees. As this development is still in full swing, it requires no particular foresight to state that volume 6 of Ullmann will probably be the first one to become out of date. This applies particularly to those sections in which the legal prescriptions form the starting point of the account of the subject, as in the chapter on safety techniques (110 pp.). In contrast to this, in the majority of the chapters on environmental protection the problems and their possible technical solution are in the foreground. Particular mention must be made of the chapter on ecologically unobjectionable production processes (67 pp.). After a short introduction, the volume begins with four chapters on some general matters, namely ecology (22 pp.), legal principles (19 pp.), endangering of the environment (14 pp.), and toxicology (90 pp.). The already mentioned chapter on ecologically unobjectionable processes is followed by individual areas of environmental protection, namely prevention of atmospheric pollution (96 pp.), effluents (144 pp.), soil (61 pp.), wastes (99 pp.), and noise prevention (56 pp.). Corresponding to its importance, a relatively broad account is given of the biological treatment of effluents; for example, nine different plants that have been realized in practice are described. In comparison with this, the anaerobic treatment of effluents, which is finding increasing interest, is discussed relatively briefly. Here a reference to "Methane" in vol. 16 would have been appropriate.

The coordination of the contributions to this volume was particularly difficult because of the great breadth and complexity of the field. It can nevertheless be stated that, in spite of the very large number of participating authors (about 100), the editors have succeeded well in this task.

Volume 20, the second volume to be reviewed here, belongs to the alphabetical part of Ullmann. Accordingly, it contains headings from a wide diversity of areas, for example nitric acid and related compounds (58 pp.), hydrochloric acid (12 pp.), oxygen and ozone (25 pp.), rhenium, rubidium (including their compounds), resorcinol, salicyclic acid, saponins, and radionuclides (90 pp.), of which, however, the most important—plutonium, thorium, the transuranics and uranium—have their own headings. In addition to these chemically oriented entries there are application-oriented ones: rocket fuels (22 pp.), reactive dyestuffs (11 pp.), reduction (21 pp.), cleaning agents (without detergents) (10 pp.), reproduction technology (22 pp.), reprography (10 pp.), scents and aromas (89 pp.), rodenticides used for plant protection, foam suppression, foamed plastics (18 pp.), hypnotics (16 pp.), abrasion, abrasives agents, and lubricants (215 pp.), chocolate (16 pp.), shoe-cleaning agents, and protective gases. These application-oriented entries obviously also contain a large amount of chemistry; thus, under the heading of scents and aromas some hundreds of compounds are described.

In the quality of presentation and in their arrangement these two volumes are equivalent in every respect to those already in existence. The amount of work that the authors, editors, and publishers have put into them is shown by the fact the preliminary work on the next (5th) edition of Ullmann has already been started, even though the present edition will not be completed before the end of next year. The new edition will, moreover, be in English.

Ulfert Onken [NB 566 IE]

[*] See *Angew. Chem. 94* (1982) 228, *Angew. Chem. Int. Ed. Engl. 21* (1982) 387.

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 (Federal Republic of Germany).

Organische Spurenanalyse. By *K. Beyermann*. Thieme, Stuttgart 1982. *ca.* 240 pp., bound, DM 98.00.—ISBN 3-13-617901-3

Mykologie. Grundriß für Naturwissenschaftler und Mediziner. By *E. Müller* and *W. Loeffler*. Thieme, Stuttgart 1982. Revised and supplemented fourth edition. *ca.* 368 pp., bound, *ca.* DM 36.00.—ISBN 3-13-436804-8

Applied Physics Communications. Vol. 1. Edited by *A. M. Hermann* and *J. A. Woollam*. Marcel Dekker, New York 1981. 120 pp., bound, $ 63.50 (institutional rate), $ 31.75 (individual rate).—ISSN 0277-9374

The Chemistry of Soil Processes. Edited by *D. J. Greenland* and *M. H. B. Hayes*. John Wiley, Chichester 1981. 714 pp., bound, £ 36.00.—ISBN 0-471-27693-6

Introduction to Organic Chemistry. By *D. Applequist, C. De Puy,* and *K. L. Rinehart.* John Wiley, Chichester 1982. Third edition, xiii, 384 pp., bound, £ 16.25.—ISBN 0-471-05641-3

NATO Advanced Study Institutes Series. Series B: Physics. Vol. 73: Scattering Techniques Applied to Supramolecular and Nonequilibrium Systems. Edited by *S.-H. Chen, B. Chu,* and *R. Nossal.* Plenum Press, New York 1981. xiv, 928 pp., bound, $ 95.00.—ISBN 0-306-40828-7

Diccionario Técnico de Plásticos. Kunststofftechnisches Wörterbuch. Vol. V: Spanisch-Deutsch. By *A. M. Wittfoht* and *A. Rubin.* Carl Hanser Verlag, München 1981. xvi, 496 pp., bound, DM 98.00 (subscription price when purchasing Vol. VI: Deutsch-Spanisch: DM 88.00).—ISBN 3-446-10364-3

Dynamic NMR Spectroscopy. By *J. Sandström.* Academic Press, New York 1982. x, 226 pp., bound, $ 39.50.—ISBN 0-12-618620-0

Oxygen and Oxy-Radicals in Chemistry and Biology. Edited by *M. A. J. Rodgers* and *E. L. Powers.* Academic Press, New York 1981. xiii, 808 pp., bound, $ 54.00.—ISBN 0-12-592050-4

Wood Combustion—Principles, Processes and Economics. By *D. A. Tillman, A. J. Rossi,* and *W. D. Kitto.* Academic Press, New York 1981. x, 208 pp., bound, $ 19.50.—ISBN 0-12-691240-8

Trace Analysis. Vol. 1. Edited by *J. F. Lawrence.* Academic Press, New York 1981. ix, 331 pp., bound, $ 39.50.—ISBN 0-12-682101-1

Enzyme. Bezugsquellen, Daten, Eigenschaften. By *P. Pfaender.* Gustav Fischer Verlag, Stuttgart 1982. ix, 313 pp., bound, DM 59.00.—ISBN 3-437-30353-8

Advances in Polymer Science. Vol. 43: Polymerizations and Polymer Properties. Edited by *H.-J. Cantor, G. Dall'Asta, K. Dušek, J. D. Ferry, H. Fujita, M. Gordon, J. P. Kennedy, W. Kern, S. Okamura, C. G. Overberger, T. Saegusa, E. V. Schulz, W. P. Slichter,* and *J. K. Stille.* Springer-Verlag, Berlin 1982. v, 252 pp., bound, DM 112.00.—ISBN 3-540-11048-8

Hazard Assessment of Chemicals. Current Developments. Vol. 1. Edited by *J. Saxena* and *F. Fisher.* Academic Press, New York 1982. xii, 461 pp., bound, $ 49.50.—ISBN 0-12-312401-8

Some Thermodynamic Aspects of Inorganic Chemistry. By *D. A. Johnson.* Cambridge University Press, Cambridge 1982. Second edition, 282 pp., bound, £ 18.00 (hard cover)/£ 6.95 (paperback).—ISBN 0-521-24204-5/0-521-28521-6

Waste Treatment and Utilization. Theory and Practice of Wash Management. Vol. 2. Edited by *M. Moo-Young, C. W. Robinson,* and *G. J. Farquhar.* Pergamon Press, Oxford 1982. xxi, 565 pp., bound, $ 83.00.—ISBN 0-08024012-7

Nonisotopic Alternatives to Radioimmunoassay. Principles and Applications. Edited by *L. A. Kaplan* and *A. J. Pesce.* Marcel Dekker, Basel 1981. xi, 342 pp., bound, SFr 135.00.—ISBN 0-8247-1581-9

Perspective in Catalysis. Edited by *R. Larssen.* Liber Läromedel, Malmö 1981. 122 pp., bound, SKr 80.00.—ISBN 91-40-04783-0

Advances in Quantum Chemistry. Vol. 13. Edited by *P.-O. Löwdin.* Academic Press, New York 1981. x, 251 pp., bound, $ 42.00.—ISBN 0-12-034813-6

Membrane Electrodes in Drug Substances Analysis. By *V. V. Cosofret.* Pergamon Press, Oxford 1981. xvi, 362 pp., bound, 29.50.—ISBN 0-08-026264-3

Einführung in die Neurochemie. By *F. Hucho.* Verlag Chemie, Weinheim 1982. xii, 305 pp., bound, DM 78.00.—ISBN 3-527-25929-5

Flavor Research. Recent Advances. Edited by *R. Teranishi, R. A. Flath,* and *H. Sugisawa.* Marcel Dekker, Basel 1981. x, 381 pp., bound, SFr 168.00.—ISBN 0-8247-6568-0

Chimica—Ein Wissensspeicher. Band I. Anorganische Chemie, Organische Chemie. By *H. Keune, M. Augustin, D. Demus,* and *E. Traeger.* Verlag Chemie, Weinheim 1981. 506 pp., bound, DM 45.00.—ISBN 3-527-25906-6

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Diastereogenic Addition of Crotylmetal Compounds to Aldehydes**

By Reinhard W. Hoffmann*

Dedicated to Professor Georg Wittig on the occasion of his 85th birthday

In an ideal synthesis, the formation of the CC bonds as well as the creation of the chiral centers and of the final functionality would be carried out simultaneously in each step. Accordingly, stereoselective CC bond forming reactions are required. Instead of a pair of diastereomers, a synthesis should yield only one of the two possible diastereomers. Such selectivity is often achieved in the addition of crotylboron, -aluminum, -tin, -titanium, and -chromium compounds to aldehydes. Depending on whether one starts from *E*- or *Z*-crotyl compounds, one diastereomeric adduct is formed preferentially. In this case the newly formed CC bond carries a methyl substituent. However, the synthetic goal is often a compound carrying an oxygen function at the site of the new CC bond. Compounds of this type can be obtained through addition of heteroatom-substituted allylboronic acid esters or analogous reagents to aldehydes.

1. Introduction

For several decades stereoselective synthesis belonged to the domain of alicyclic and heterocyclic chemistry, being concerned in particular with the generation of chiral centers having the desired configuration during the synthesis of sugars, steroids, or alkaloids. In contrast, stereoselective synthesis of open-chain systems has been intensely investigated only during the last few years. This surge in interest was caused by new efforts to synthesize macrolide and polyether antibiotics, as well as some pheromones containing stereochemically defined β-methyl alcohol or *vic*-diol functionalities. Many improvements have been reported within a short span of time and numerous methods are now available[1].

As an example, consider some syntheses of *exo*-brevicomin **3**, which is a sex-attractant of the bark beetle *Dendroctonus brevicomis*. Being a bicyclic acetal, brevicomin can be prepared from the ketodiol **2**. Diastereomerically pure **2**[***] is needed in order to obtain isomerically pure **3**. Following a classical synthetic strategy[2] the carbon skeleton would be constructed first. In the case of **1** this would involve the synthesis of the stereochemically uniform *cis*-substituted double bond constituting the two adjacent prochiral centers. Further steps—epoxidation with *m*-chloroperbenzoic acid and opening to the *trans*-diol **2**—give rise to the two neighboring chiral centers with the desired relative configuration *via* "internal asymmetric induction"[1].

In such a typical reaction sequence the carbon skeleton is first formed, followed by creation of uniform prochirality, and finally of the chiral centers themselves. In princi-

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[**] Based on a plenary lecture given at the GDCh Hauptversammlung in Hamburg on September 19, 1981.

[***] In this article only one enantiomer of the diastereomers is shown in each case.

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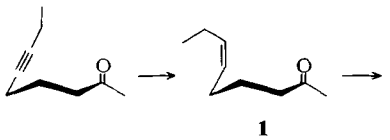

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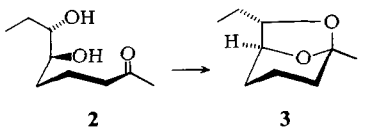
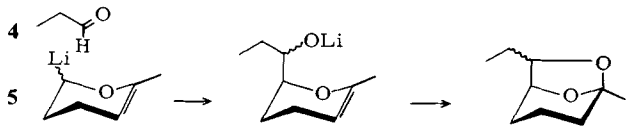


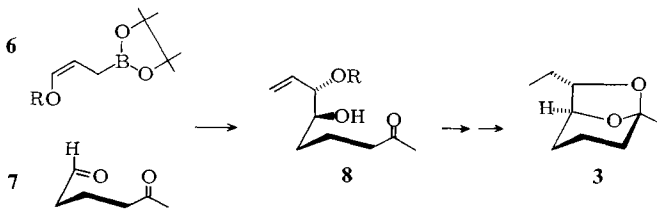
2 3

ple, it would be more economical if the carbon atom skeleton and the chiral centers were formed in a single step. For this purpose, two prochiral C atoms would have to be linked to each another, *e.g.* the negatively charged C atom in the organolithium compound **5** and the C atom of the carbonyl group in the aldehyde **4**. However, this reaction sequence did not give the desired diastereomer only, but rather a mixture of the two possible diastereomers in the ratio 1 : 1.3[3].



3 + Diastereomer

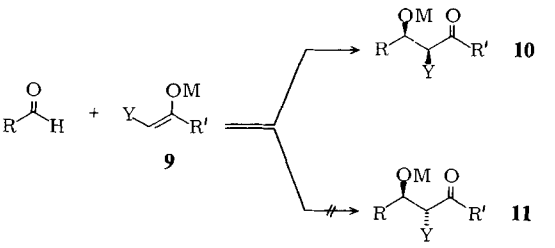
CC bond forming reactions of much greater diastereoselectivity are, therefore, required. This holds, for example, for the addition of the allylboronic acid esters **6** to the aldehyde **7**, which resulted in a diastereoselectivity of 15 : 1 in favor of the required adduct **8**. This, in turn, was easily converted into *exo*-brevicomin **3**[4].



8 **3**

This example illustrates the trend in present day stereoselective synthesis to form not only a new CC bond *but also* the relative (and possibly also the absolute) configuration of the newly formed chiral centers in a single reaction step. Thus, by avoiding refunctionalization steps one approaches the "ideal synthesis"[5] in which individual segments of the molecular skeleton are linked in such a way that the final functionality and steric structure are formed simultaneously. Because of the high selectivity (> 100 : 1)[10, 11] in the aldol addition of metal enolates **9** to aldehydes, this diastereogenic CC bond forming reaction[6, 7] is of particular current interest[1, 7-9].

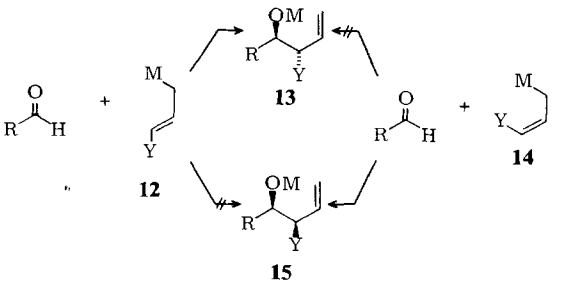
It took a considerable length of time, however, before the early observations of *Dubois et al.*[12] and *House et al.*[13] were developed so that the aldol addition could be carried out in such a way that of the two possible diastereomeric adducts **10** and **11**, only one—*e.g.* **10**, and not **11**—is formed (Scheme 1).



9 **10** **11**

Scheme 1. Y = alkyl or a heteroatom-bonded group, M = metal.

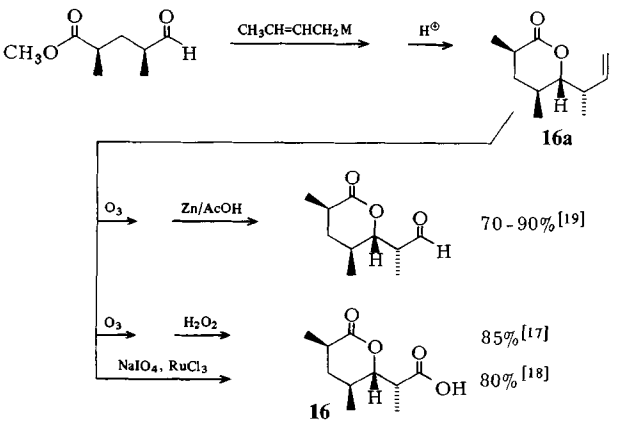
The addition of allylmetal compounds to aldehydes (Scheme 2) is structurally and, probably also, mechanistically analogous to the aldol addition (Scheme 1). Accordingly, in the case of the reaction of aldehydes with allylmetal derivatives **12** or **14**, a high degree of diastereoselectivity is achieved. Because reactions of this kind are only marginally covered in reviews of aldol additions[1, 7-9] it is appropriate at this point to review them in their own right[14].



12 **13** **14** **15**

Scheme 2. Y = alkyl or a heteroatom-bonded group, M = metal.

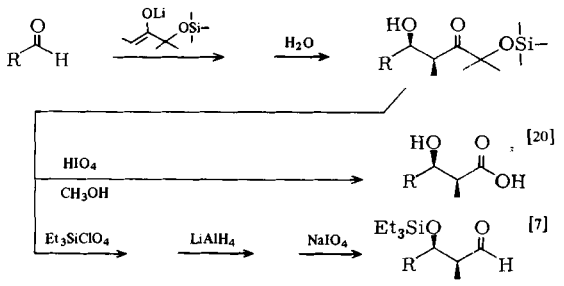
These reactions are not only structurally, but also synthetically equivalent to the aldol addition since the adducts **13** and **15**, being homoallylic alcohols, can be transformed into aldol derivatives. The newly formed alcohol group is often protected by esterification in these reactions. The double bond is cleaved by ozonolysis and transformed into



Scheme 3.

an alcohol or an aldehyde by reductive work-up[15]. Oxidative work-up, on the other hand, leads to formation of carboxylic acids[16]. Typical examples are given by the transformations of a cyclic lactone-olefin[17-19] **16a** which led to the Prelog-Djerassi lactone **16** (Scheme 3).

These refunctionalizations turned out not to be more bothersome than the corresponding reactions required after aldol addition of special enolate reagents to aldehydes (Scheme 4).



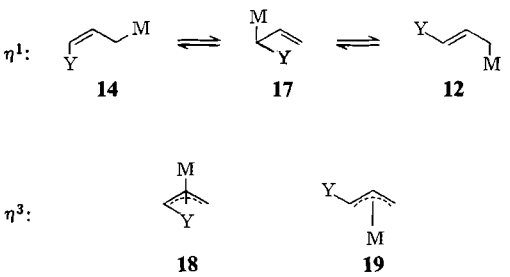
Scheme 4.

At this point a word on the stereo-nomenclature of diastereomeric pairs, such as **10/11**, is in order. If one attempts to read the original literature on aldol additions quoted in the reviews[1,7-9], one is confronted with a Babylonic confusion. The unambiguous *R*,S**-nomenclature is too cumbersome for easy reading of formulas and for verbal communication. Research groups concerned with the aldol addition predominantly use the terms *threo* for **11** and *erythro* for **10**[7,20]. Unfortunately, this designation is just the opposite of what would result from the usual Fischer projection. Therefore, when using the terms *erythro* and *threo* it is first necessary to establish to which nomenclature forms the audience is accustomed. Because of this dilemma, other designations have been suggested. These are derived either from structures of the products, such as *u/l*[21], *syn/anti*[22], *p/n*[23], or from the structures of the educts, such as *lk/ul*[21], *rere/resi*[7,24,25], or heterofacial/homofacial[24]. Although none of these descriptions is ideal, the *syn/anti* nomenclature will be used here for the sake of ease of communication, because in the most frequently encountered simple cases structures can be recognized or assigned at a glance. Thus **10** would be a *syn* compound, because in the "sawhorse" formalism the groups of interest, OM and Y, are on the same side of the main backbone (the newly formed CC bond).

2. Configurational Stability of Allylmetal Compounds

In the addition reactions in Scheme 2, the basic idea is the production of a specific relative configuration in the product by transformation of the prochirality of the allylmetal compound, *e.g.* *E* in **12**, or *Z* in **14**, in a stereoselective reaction. Therefore, a preparative application is usually possible only when each *E/Z* stereoisomer of the γ-substituted allylmetal compound is independently accessible. Furthermore, each of these should be configurationally stable under the reaction conditions and, ideally, also on storage.

Allylmetal compounds can exist as either *monohapto*-(η^1-) or *trihapto*-(η^3-) bound forms, each of which should be configurationally stable. However, *E/Z* isomerization is possible for the *monohapto*-compounds **12** and **14** *via* a metallotropic rearrangement to **17**. Typical examples of this are the fluxional dialkyl(allyl)boron compounds[26,27]. The transition states for these rearrangements should resemble the *trihapto*-structures **18** and **19** ($M=BR_2$). *E/Z*-isomerizations are also conceivable with the *trihapto*-compounds **18** and **19**, if the *monohapto*-structure **17** is accessible from them. For example, this is the case in allyllithium compounds[28,29] where rapid *E/Z* isomerization occurs[30,31].



In a simplified discussion it is not necessary to consider the ion-pair character of allylmetal compounds. Rather, it suffices to state that, in order to be of use for diastereoselective CC bond formation, only allylmetal compounds possessing an energy barrier >20 kcal/mol for the mutual interconversion of the *monohapto*- and *trihapto*-forms can be used. Examples of *trihapto*-compounds fulfilling this requirement are dicarbonyl(cyclopentadienyl)iron derivatives[32], a wide range of nickel complexes[33], or dicyclopentadienyltitanium compounds[34]. Allylpotassium compounds should also be mentioned here[29,35]. Among the *monohapto*-allylmetal compounds, the silanes should have the lowest tendency to metallotropic isomerization[36]. The configurational stability decreases on going from the germanium to the tin compounds[37,38], which often undergo *E/Z* isomerization below 100 °C or in the presence of Lewis bases.

Of the allyl compounds of the third group elements, those of boron are the best known. In such compounds the tendency to metallotropic rearrangement can be controlled through proper choice of the other substituents at boron: dialkyl(allyl)boron compounds rearrange rapidly at room temperature[26,27] and can be handled without isomerization only below −78 °C[39]. π-Donor substituents at boron raise the energy of the vacant boron p orbital to such an extent that rearrangement to the *trihapto*-structure is rendered difficult or does not occur. Although a single OH group at boron is insufficient to suppress the borotropic shift at −20 °C[40], an amine substituent renders the compounds stable up to 150 °C[41].

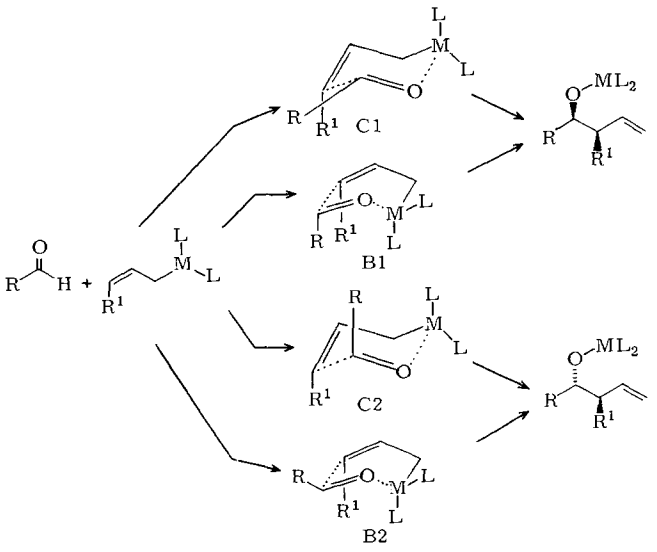
Allylboron derivatives with two oxygen functions at boron, *e.g.*, the crotylboronic acid esters **25** and **26**, are sufficiently thermally stable that the *E*- and *Z*-derivatives are separately manipulable at room temperature[42-44]. Consequently, allylboron compounds containing one oxygen and one nitrogen substituent, or even two nitrogen substituents,

are particularly resistant to borotropic rearrangement[44,45]. On the other hand, with these compounds and the allylboronic acid esters as well, the tendency to isomerize like other organometallic compounds in the presence of Lewis acids[44-46] becomes apparent; this, of course, limits the choice of conditions for their preparation.

Allylmagnesium, like the organozinc compounds—and by inference also the organocadmium compounds—undergo rapid metallotropic shifts **12** ⇌ **14**, even at low temperatures[30,47]. Thus, apart from special cases[48,49], they are hardly useful as reagents in diastereoselective additions to aldehydes[50,51]. The same holds[52] for the allyllithium compounds[30,53], particularly if not only one of the stereoisomers **12** or **14** is to be used. Consequently, further discussion will be limited to allylmetal compounds which are configurationally stable *per se* at room temperature and also under the conditions of reactions with the aldehydes. *Monohapto* bonded allylchromium[54,55], allylzirconium[56], and allyltitanium compounds[57,58] also belong to this class.

3. Stereochemistry of the Addition Reaction

An allylic rearrangement is always observed in reactions between allylmetal compounds such as **12** or **14** and aldehydes under kinetically controlled conditions (Scheme 2). Thus, it is reasonable to propose a six-membered cyclic transition state, especially when the metal can coordinate to the carbonyl group of the aldehyde as a Lewis acid due to the presence of a low-lying vacant orbital, *i.e.* when it is able to form ate-complexes[59]. In order to delineate the occurrence and the limits of diastereoselectivity one can refer to the concepts used in the interpretation of the aldol reaction[8,9]. As in the aldol addition, the transition state comprises a cyclic arrangement of the reacting atoms with conformations similar to that of cyclohexane, *i.e.* chair or boat. Thus, diastereoselectivity depends on the relative energies of the diastereomeric transition states and these can be influenced by conformational factors in the same way as in cyclohexane. This is illustrated (cf. [8]) for the addition of a *Z*-allylmetal derivative to an aldehyde. Both, the chair-like transition states C1 and C2, as well as boat-like transition states B1 and B2 are considered in Scheme 5.



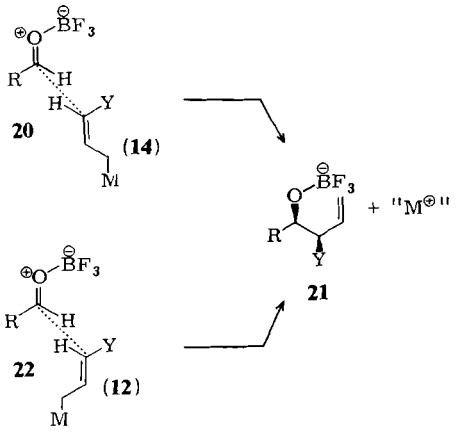
Scheme 5. C1, C2 = chair-like, B1, B2 = boat-like transition states.

In the simplest case the addition is diastereoselective when one of the transition states is approximately >2 kcal/mol more stable than the others. For the discussion of the factors determining the relative energies of the transition states it is necessary to assume that at least two more ligands, L, are bound to the metal. The steric requirements of R and L are of decisive importance for the diastereoselectivity, because in the chair-like transition state C2 a 1,3-diaxial interaction exists between them. If this interaction is larger than the *gauche*-interaction between R and R^1 in the transition state C1, then C1 will be preferred. Of the three conceivable boat-like conformations, the one having the aldehyde-oxygen and the allyl-CH groups in the bow and stern positions are preferred. Only these transition states (B1 and B2) are considered here. Of these, transition state B2 should be significantly more stable than B1 as a result of the 1,3-diaxial R/L and R/R^1 interactions. However, because of the eclipsing groups, boat transition states are inherently disfavored with respect to the chair transition states. However, the energy difference between boat and chair transition states should not be very large, since studies of the Claisen rearrangement, which takes place *via* similar transition states, have shown that the boat-like transition states are only 2—3 kcal/mol less stable than the corresponding chair forms[60]. Therefore, boat-like transition states may well represent the principal path of the Claisen rearrangement as a result of steric interactions between substituents[1]. Consequently, boat-like transition states should also be considered in the additions of allylmetal compounds discussed here.

These conclusions were derived for the reactions of the *Z*-allylmetal compounds **14**. A similar analysis may be made for the reactions of the corresponding *E*-compounds of type **12**.

Further points to be noted include: a high degree of diastereoselectivity may be expected in additions to aldehydes, but not to ketones, because the diastereoselectivity stems from different steric interactions between the groups R and the aldehydic H with the metal ligands. Therefore, the size of L should be significant for the degree of diastereoselectivity. Fortunately, the size of L can be chosen at will (see *e.g.* [61]). The R/L-interaction and, hence the diastereoselectivity are at a maximum when the length of the oxygen-metal bond in the transition state is at a minimum. This will be the case in endothermic or weakly exothermic reactions in which the transition state occurs late on the reaction coordinate[62]. However, the ultimate attainable metal-oxygen bond length is the most decisive factor. According to this criterion, as shown by *Evans et al.*[8], diastereoselectivity should decrease along the series, metal = B (B—O ≅ 1.4 Å), Si (Si—O ≅ 1.6 Å), Ti (Ti—O ≅ 1.7 Å), Sn (Sn—O ≅ 2.1 Å), Zr (Zr—O ≅ 2.1 Å). The above considerations refer to metals which can coordinate to the aldehydic carbonyl group as Lewis acids. It is questionable whether or not this is possible for M = $R_3B^{\ominus}$ [63]. If so, this reaction would imply a nucleophilic substitution with retention at a saturated first row element (boron).

The addition of allylmetal compounds to aldehydes can, according to the nature of the metal, occur even at low temperatures, or, in the case of trialkyltin derivatives, only at temperatures above 100 °C[64]. Such additions are catalyzed by Lewis acids such as boron trifluoride etherate[65]. Essentially only the Lewis acid catalyzed addition is known for allyltrialkylsilanes[66]. The catalysis may derive from an activation of the carbonyl group through coordination of the Lewis acid with the oxygen atom. In these cases it is not certain whether the reactions still take place *via* cyclic transition states since the aldehyde group is already complexed with the catalyst. In these cases open-chain transition states as in S_E2'-reactions may well be more favorable than cyclic ones[67]. Support for this interpretation comes from the fact that allylic rearrangement is no longer the rule in catalyzed additions of crotyltin compounds to quinones[68], because both S_E2' and S_E2 reactions are possible for open-chain transition states[68]. Of such open-chain transition states (see **20** and **22**) the most



favorable will be those in which the least steric interaction occurs along the newly formed bond. Stereoconvergence can occur in such cases, so that predominantly one and the same diastereomeric product **21** arises from the two stereoisomeric allylmetal compounds **12** and **14**.

4. Diastereogenic CC Bond Formation

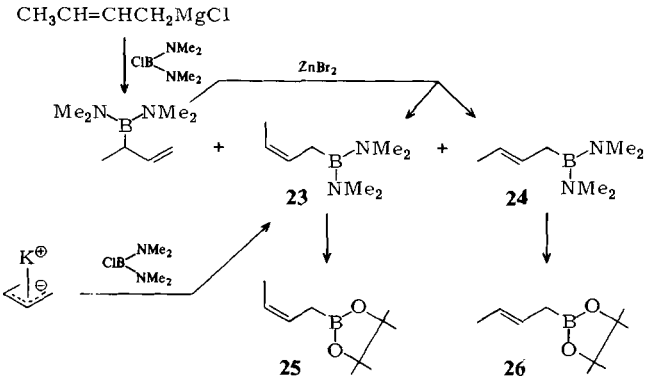
In this section we will describe the preparative aspects of the addition of crotylmetal compounds to aldehydes, considering the synthesis of the stereochemically pure reagents as well as the diastereoselectivity in their reactions with aldehydes.

4.1. Boron as Key Atom

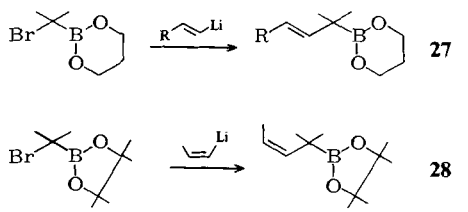
4.1.1. Crotylboronic Acid Esters

The crotylboronic acid esters **25** and **26** can be prepared from the reaction of crotylmagnesium chloride with chlorobis(dimethylamino)borane, which gives a mixture of isomeric methylallylboronic acid amides[45]. Isomerization with $ZnBr_2$ at 120 °C gives a mixture of **23** and **24**, which can be separated by distillation at 100 torr using a spinning band column.

Pure *Z*-crotylbis(dimethylamino)borane **23** has also been obtained from *Z*-crotylpotassium; the yields were *ca.* 40%[44]. The boronic acid amides **23** and **24** could be converted *in situ* with a 1,2-diol into the reactive but thermally only slightly stable boronic acid esters **25** and **26**[44]. Analogous chiral crotylboronic acid esters (e.g. **67** and **69**) are



obtainable using optically active 1,2-diols[69]. The dimethyl ester of *Z*-crotylboronic acid can be advantageously generated *in situ* from *Z*-crotylpotassium[70] and allowed to react directly with aldehydes. *E*- and *Z*-Boronic acid esters such as **27** and **28** carrying two α-alkyl groups, *e.g.* CH_3, can be obtained in good yields from α-bromoisopropylboronic acid esters[42,44].



The crotylboronic acid esters thus obtained undergo virtually quantitative addition to aldehydes below 0 °C[71]. Cleavage of the boric acid esters formed using triethanolamine gives rise to the homoallylic alcohols **29** and **30**, the 1,2-diol, and the boratrane **31**. In favorable cases the homoallyl alcohol and the diol can be separated by distillation. If this is not possible, the homoallyl alcohol must be separated by gas or column chromatography.

In the addition of the *Z*-crotylboronic acid ester **25** to aldehydes, the diastereoselectivity obtainable was directly related to the isomeric purity of **25** (see Table 1)[44,70]. In each case the diastereomer of type **29** predominated; this is formed *via* the chair-like transition state C1. This stereoselective CC bond formation has been applied in the preparation of the pheromone **33** of the drugstore beetle, whereby the *syn*-isomer **32** was obtained in 70% enantiomeric excess (e.e.)[*] using the chirally modified crotylboronic acid ester **69**[16] (Scheme 6).

[*] e.e., enantiomeric excess is a measure of the enrichment of one enantiomer relative to a racemic mixture. A 70% e.e. corresponds to a 85% content of the enantiomer concerned. Here, diastereomeric purity refers to the amount of the appropriate diastereomer in the isomeric mixture isolated.

The addition of the *E*-crotylboronic acid ester **26** to aldehydes also took place in a diastereoselective manner *via* transition state C1 (see Table 1). Thus, the complementary

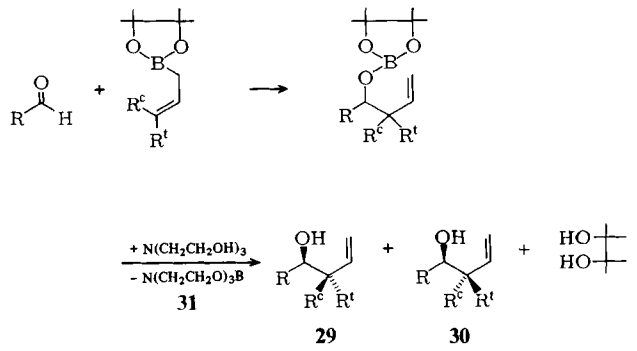
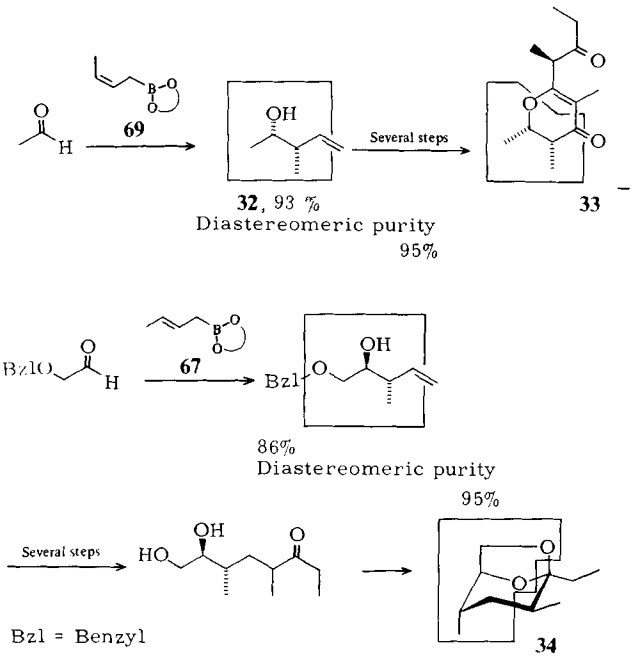


Table 1. Diastereoselectivity in the formation of the homoallylic alcohols **29** and **30**.

Aldehyde R	Boronic Acid Ester	R^c	R^t	Yield [%]	**29** : **30**	Ref.
C_6H_5	**25**	CH_3	H	80	96 : 4	[44]
CH_3				40	97 : 3	[44]
C_2H_5				62	97 : 3	[44, 70]
$(CH_3)_2CH$				59	96 : 4	[44]
$C_2H_5(CH_3)CH$				98	>95 : <5	[69]
C_6H_5	**26**	H	CH_3	22	94 : 6	[44]
CH_3				20	93 : 7	[44]
C_2H_5				26	93 : 7	[44]
$(CH_3)_2CH$				51	96 : 4	[44]
C_6H_5	**6a**	CH_3O	H	86	>95 : <5	[72]
CH_3				85	93 : 7	[72]
C_2H_5				94	92 : 8	[72]
$(CH_3)_2CH$				94	89 : 11	[72]
C_6H_5	**6b**	CH_3OCH_2O	H	82	>95 : <5	[4]
CH_3				89	92 : 8	[4]
C_2H_5				88	89 : 11	[4]
$(CH_3)_2CH$				90	80 : 20	[4]
C_6H_5	**6c**	CH_3 | CH_3OCO | CH_3	H	93	94 : 6	[4]
CH_3				86	88 : 12	[4]
C_2H_5				88	80 : 20	[4]
$(CH_3)_2CH$				57	68 : 32	[4]
C_6H_5	**36**	H	OCH_3	87	95 : 5	[72]
CH_3				76	95 : 5	[72]
C_2H_5				68	95 : 5	[72]
$(CH_3)_2CH$				77	>98 : <2	[72]
C_6H_5	**37**	CH_3S	H	95	98 : 2	[73]
$(CH_3)_2CH$				90	95 : 5	[73]
C_6H_5	**39**	H	$(CH_3)_3Si$	89	>98 : <2	[74]
n-C_7H_{15}				78	>98 : <2	[74]
$AcO(CH_2)_8$				92	>98 : <2	[74]

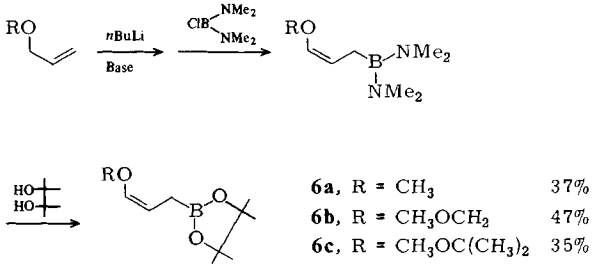
diastereoselectivity afforded the homoallyl alcohols with *anti*-configuration. This CC bond formation step was used in a synthesis of δ-multistriatin **34**, whereby 52% e.e. (= 76% of the corresponding enantiomer) was achieved using the chirally modified crotylboronic acid ester **67**[15] (Scheme 6). Furthermore, the α,α-disubstituted boronic acid ester **28** also added to benzaldehyde with 97% diastereoselectivity[44].



Scheme 6.

4.1.2. Substituted Boronic Acid Esters

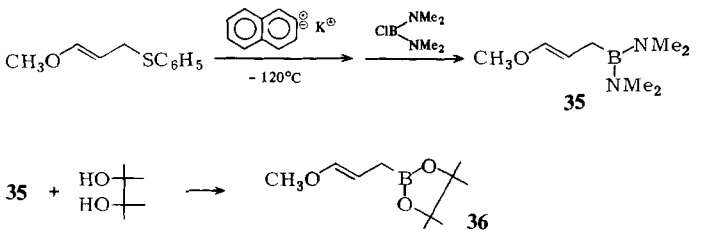
Diastereoselective CC bond formation also occurs using γ-alkoxy-substituted allylboronic acid esters: the *Z*-allylboronic acid esters **6**, prepared according to Scheme 7, add to aldehydes at room temperature (cf. Table 1)[4, 72, 75].



Scheme 7. Tetramethylethylenediamine or potassium *tert*-butoxide is used as a base.

An application of this reaction has already been given in Section 1 (the synthesis of *exo*-brevicomin **3**). However, the reaction between **6a** and isobutyraldehyde took place with somewhat lower diastereoselectivity than in the reactions with benzaldehyde, acetaldehyde, and propionaldehyde. This decrease in diastereoselectivity is even more pronounced in the addition of the allylboronic acid esters **6b** and **6c** possessing larger γ-substituents, particularly in the reaction with sterically hindered aldehydes. These limiting factors can be understood in terms of transition states C1 and C2: sterically demanding groups R and R^1 destabilize C1 in particular, and to a lesser extent C2. In the latter case, the two groups are farther removed from each other. As a consequence, a significant portion of the reaction will take place *via* transition state C2 when steric hindrance is present. The results do not preclude the possibility that the boat-like transition state B2 can also be involved in the reaction.

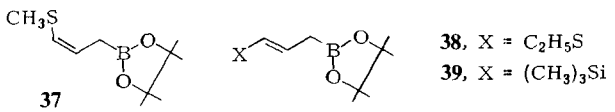
In the addition of boronic acid esters of *E*-configuration such as **36**, the same steric factors which decrease the diastereoselectivity with sterically demanding aldehydes, such as in reactions of **6**, should now increase the diastereoselectivity. Scheme 8 shows the synthesis of **36**.



Scheme 8.

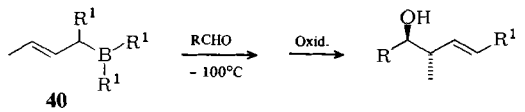
E-Methoxyallylpotassium generated at $-120\,^{\circ}C$ can be trapped *in situ* giving **35**. Under these conditions, isomerization to the *Z*-conformer is largely suppressed: the product **36** was formed in 60% total yield and with 90% *E*-configuration. Since **36** reacts more rapidly with aldehydes than the *Z*-isomer **6a**, crude **36** was mixed with 0.9 equivalents of the aldehyde, whereby virtually only **36** reacted. The data in Table 1 demonstrate the high diastereoselectivity obtainable in these reactions, particularly in the addition to isobutyraldehyde.

γ-Alkylthioallylboronic acid esters **37** and **38** can be prepared analogously and also add with high diastereoselectivity to aldehydes[73]. Using a mixture of **38** and its *Z*-isomer, the more reactive *E*-isomer **38** reacted selectively with a slight deficiency of the aldehydes[73]. The silyl-substituted boronic acid ester **39** also adds diastereoselectively to aldehydes[74].



38, X = C_2H_5S
39, X = $(CH_3)_3Si$

With respect to reactions of other crotylboron compounds, the reaction between **40** and aldehydes is worthy of mention since a borotropic isomerization can be avoided when the reaction is carried out at $-100\,^{\circ}C$[39].

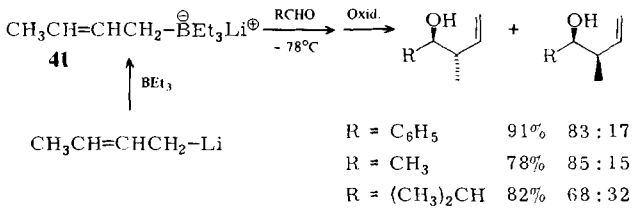


R = C_6H_5, R^1 = *n*Bu		84%
R = C_6H_5, R^1 = Et		67%
R = $C_6H_5CH_2CH_2$, R^1 = Et		52%

As expected, dialkylcrotylboranes which are not configurationally stable at room temperature react with aldehydes in a nonstereospecific manner[76].

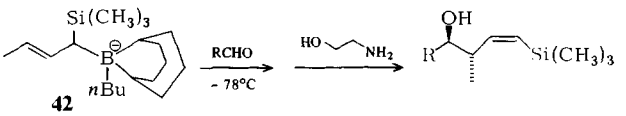
4.1.3. Crotylborate Complexes

The situation is different in the reaction of the trialkylcrotylborate complex **41**. Due to the method of preparation, this complex probably contains *ca.* 80% *E*-crotyl residues. This was also the maximum diastereoselectivity observed[63,77].



R = C_6H_5	91%	83 : 17	
R = CH_3	78%	85 : 15	
R = $(CH_3)_2CH$	82%	68 : 32	

The higher degree of isomeric purity in educt **42** (and its stannyl analogues) led to very high diastereoselectivities in the addition to aldehydes; however, due to side reactions the chemical yields were only 50—70%. On the other hand,

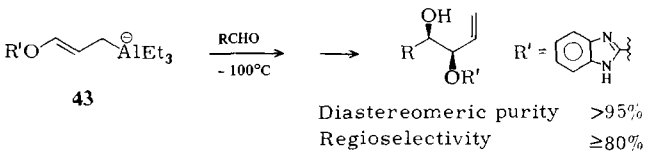


R = C_6H_5	50%	Diastereomeric	>98%
R = *n*Bu	62%	purity	>98%

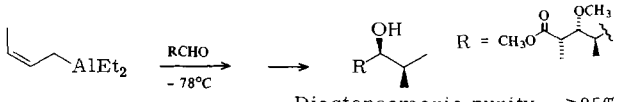
42 (pyridinium instead of butyl) gave very high chemical yields and diastereomeric purities of between 85 and 90%[78].

4.2. Crotylaluminum Compounds

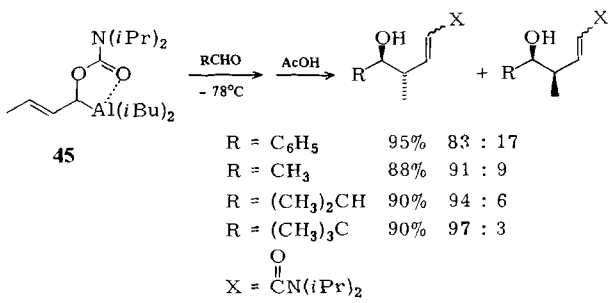
Aluminate complexes can be obtained by analogy to **41**. However, the reaction of these complexes with aldehydes did not give rise to a particularly high degree of diastereoselectivity[63,77]. This is probably due to the fact that the double bond in crotyl- and heterosubstituted allylaluminates[79] does not possess a uniform configuration; however, diastereoselective addition to aldehydes has been achieved with some heterosubstituted allylaluminates, *e.g.* **43**[14,80].



Diastereomeric purity >95%
Regioselectivity ≥80%



Diastereomeric purity >95%



R = C_6H_5	95%	83 : 17	
R = CH_3	88%	91 : 9	
R = $(CH_3)_2CH$	90%	94 : 6	
R = $(CH_3)_3C$	90%	97 : 3	

X = $\overset{O}{\overset{\|}{C}}N(iPr)_2$

Crotylaluminum compounds with uniform double bond configuration, *e.g.* **44**[81], can be prepared at low temperatures from stereochemically pure crotylalkali metal compounds and react with aldehydes *in situ* in a highly stereoselective manner. In the spectacular synthesis of monensin[81], use was made of this procedure to form one of the CC bonds.

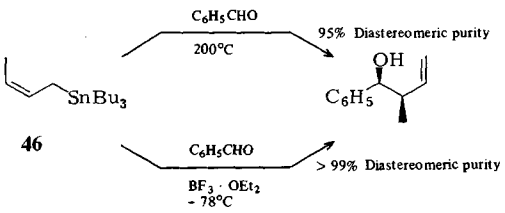
Heterosubstituted allylaluminates and allylaluminum compounds have been examined also: differing regioselectivities were observed in the addition reactions of **43**[80] and **45**[82] with aldehydes. This is possibly due to a metallotropic equilibrium in which the aluminate exists in the extended form, because of coulombic repulsion, and the aluminum compound **45** is present in an intramolecularly complexed form.

4.3. Crotylsilicon Compounds

Z-crotyl(trimethyl)silane is obtainable from butadiene[83] and *E*- and *Z*-crotyl(triphenyl)silane from the isomeric crotyl chlorides, respectively[38] (for further syntheses of trialkyl(crotyl)silanes, see [84,85]). Trialkyl(allyl)silanes of this type give good yields in the addition reaction with aldehydes only when Lewis acid catalysis ($TiCl_4$) is used[66]. The fluoride ion catalyzed addition also takes place in low yields[86]. Little information has been given about diastereoselectivity in these cases[67].

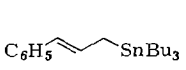
4.4. Crotyltin Compounds

Stereochemically pure crotyltin compounds can be prepared from the corresponding crotyl chlorides by reaction with trialkyl-[87] or triaryltin lithium compounds[38]. For example, **46** adds diastereoselectively to benzaldehyde at 200 °C[88]. Chloral reacts even at 20 °C[85,88].

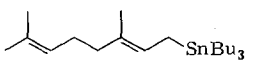


Use of the more reactive trihalotin compounds[89,90] allows a decrease in the reaction temperature. Diastereoselectivity is preserved in some cases[91]. In other cases, the dibutyl(crotyl)tin chloride adds to aldehydes in such a manner that the *E*/*Z*-ratio of the crotyl residues is no longer reflected in the *syn*/*anti* product ratio[92].

The addition of trialkyl(crotyl)tin compounds to aldehydes can also be facilitated using Lewis acid catalysts: **46** adds diastereospecifically to benzaldehyde in presence of $BF_3 \cdot OEt_2$[85]. High diastereoselectivity was also reported for the Lewis acid catalyzed addition of other γ-substituted allyltin compounds such as **47** and **48** to aldehydes[93].

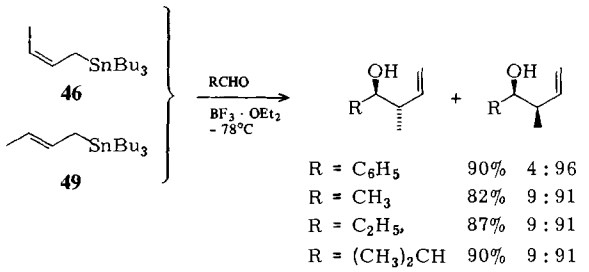


47



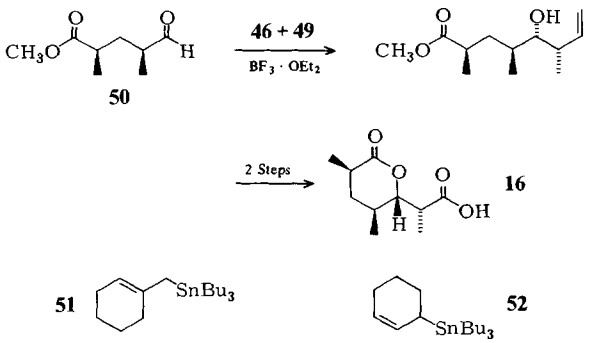
48

The *stereoconvergence* in the BF_3-catalyzed reaction was surprising: both **46** and the corresponding *E*-isomer **49** added with predominant formation of one and the same diastereomeric product[17,67]. The preparative advantage of stereoconvergence is obvious: instead of using configurationally pure starting materials, **46** or **49**, the more readily available mixture of isomers may be used. The stereoconvergence is not due to an initial rearrangement of **49** to **46**; rather, open-chain transition states have been considered as possible causes.



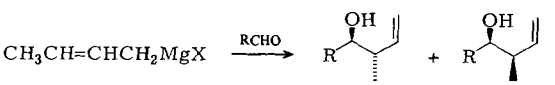
R = C_6H_5	90%	4 : 96
R = CH_3	82%	9 : 91
R = C_2H_5,	87%	9 : 91
R = $(CH_3)_2CH$	90%	9 : 91

The stereoconvergent reaction of **46** + **49** with **50** was applied to a stereoselective synthesis of the Prelog-Djerassi lactone **16**[17]. However, not all crotyltin compounds react diastereoselectively with aldehydes; thus, **51** and **52** gave mixtures of diastereomeric products[93].



4.5. Crotylmagnesium and Crotylcadmium Compounds

The addition of crotyl-Grignard compounds to aldehydes gave rise to low diastereoselectivity and are thus of little preparative interest[50,51,94]. Nontheless, some work with heterosubstituted allylcadmium compounds[48,49] indicates the possibility of diastereoselective CC bond formation.



R = C_6H_5	38 : 62
R = CH_3	50 : 50
R = C_2H_5	50 : 50
R = $(CH_3)_2CH$	57 : 43

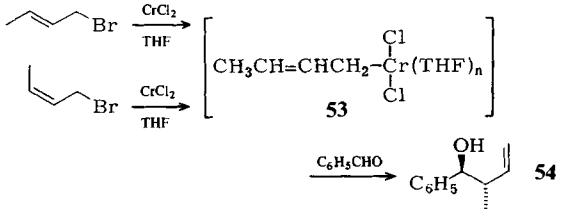
4.6. Crotyllithium Compounds

No diastereoselectivity worth mentioning has been achieved in the addition of crotyllithium to aldehydes[52].

Most likely, this is due to the fact that the lithium (like magnesium) compounds exist as equilibrating *E*/*Z*-isomers. A high degree of diastereoselectivity has occasionally been observed in the addition of γ-substituted allyllithium compounds to aldehydes[95,96]; this probably arises because the *E*/*Z*-equilibrium lies far to the side of one of the geometric isomers.

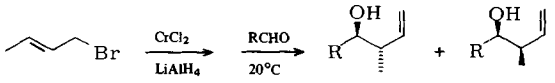
4.7. Crotylchromium Compounds

The addition of allyl bromides to aldehydes in the presence of $CrCl_2$ has been known for some time. When *E*-crotyl bromide is used, only diastereomer **54** is produced[55].



54

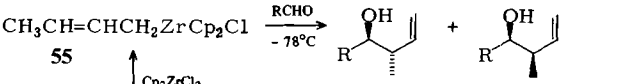
Surprisingly enough, this reaction is also stereoconvergent[54]. It is not known whether this stereoconvergence is due to an equilibration of the intermediate crotylchromium compound **53** to the *E*-isomer. The diastereoselectivity attainable depends both on the solvent (tetrahydrofuran is best) and on the aldehydic residue R[54].



R = C_6H_5	96%	100	: 0
R = n-C_3H_7	59%	93	: 7
R = $(CH_3)_2CH$	55%	95	: 5
R = n-C_5H_{11}	70%	97	: 3
R = CH_3–CH=CH	73%	83	: 17
R = $(CH_3)_3C$	64%	35	: 65

4.8. *Monohapto*-Crotylzirconium Compounds

A fair degree of diastereoselectivity is shown in the addition of the crotylzirconium compound **55** to aldehydes[56]. This may be due to the fact that the reagent, because of the method of preparation, is an *E*/*Z*-mixture.

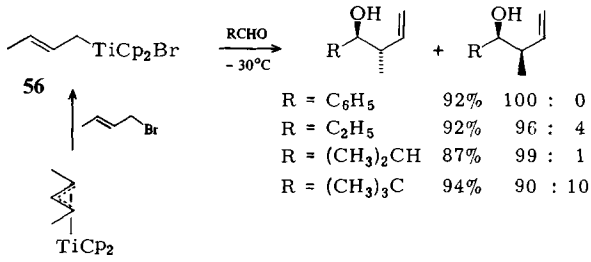


R = C_6H_5	90%	81	: 19
R = CH_3	85%	73	: 27
R = C_2H_5	88%	86	: 14
R = $(CH_3)_2CH$	90%	88	: 12
R = $CH_3O\overset{O}{\overset{\|}{C}}(CH_2)_2$	90%	94	: 6

Cp = Cyclopentadienyl

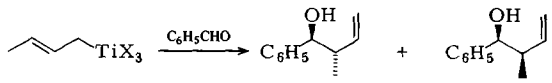
4.9. *Monohapto*-Crotyltitanium Compounds

The titanium compound **56**, which corresponds to **55**, is expected to have the *E*-configuration. Excellent diastereoselectivity was achieved in the addition of both **56** and the corresponding iodo but not the chloro complex[58].



R = C_6H_5	92%	100	: 0
R = C_2H_5	92%	96	: 4
R = $(CH_3)_2CH$	87%	99	: 1
R = $(CH_3)_3C$	94%	90	: 10

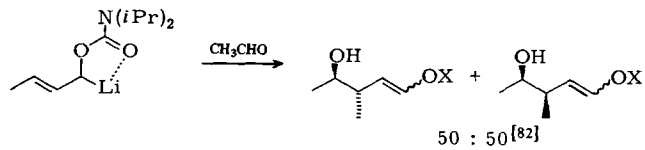
Very good yields were also reported for the addition of the triamino(crotyl)- or trialkoxy(crotyl)titanium compounds **57**—**60**[61,97]. The degree of diastereoselectivity appears to depend on both the spatial demands and the electronegativity of the residues at titanium.



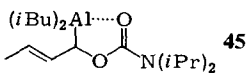
57, X = NMe_2	48 : 52[97]
58, X = NEt_2	70 : 30[97]
59, X = $OiPr$	80 : 20[61,97]
60, X = OC_6H_5	85 : 15[61]

The amino compound **58** exists as the pure *E*-compound[97]. In all likelihood, this is also true for the alkoxy-compound **60** which gave selectivities of >90% in several reactions with α-branched aliphatic aldehydes, favoring formation of the *anti*-adducts[61].

The results shown in Scheme 9 indicate that also in the case of heterosubstituted allyl derivatives, the titanium compounds are the superior reagents.

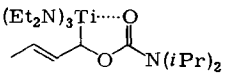


50 : 50[82]



45

91 : 9[82]



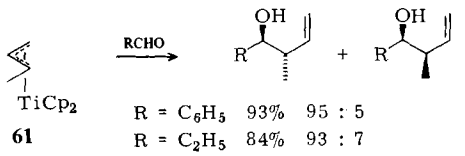
97.5 : 2.5[98]

X = $\overset{O}{\overset{\|}{C}}N(iPr)_2$

Scheme 9.

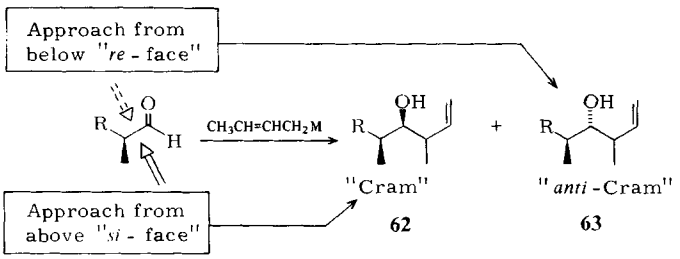
4.10. *Trihapto*-Crotyltitanium Compounds

Although stereoisomeric *trihapto*-crotylmetal derivatives are known[32,99], only titanium compounds **61** with *E*-configuration have been reacted with aldehydes to date[34]. The additions took place with good diastereoselectivity and yields.



5. Cram/*anti*-Cram Selectivity

Up until now, only those diastereogenic reactions have been discussed in which a prochiral allyl or crotylmetal compound was added to the prochiral carbonyl group of an aldehyde. The *relative* configuration of the two newly formed chiral centers was of particular interest. If the aldehyde is not achiral then the upper and lower faces of this group will no longer be an enantiotopic, but rather diastereotopic. Different diastereoisomeric adducts will be formed in CC bond formations taking place on the *re*- and *si*-faces. An example is the addition to an aldehyde containing a chiral center, such as an α-methyl group, leading to a pair of isomers such as **62**/**63** (Scheme 10) with three chiral centers. The isomers now differ as regards the configuration of the newly formed chiral center (with the hydroxy group) relative to the chiral center carried over from the aldehyde.

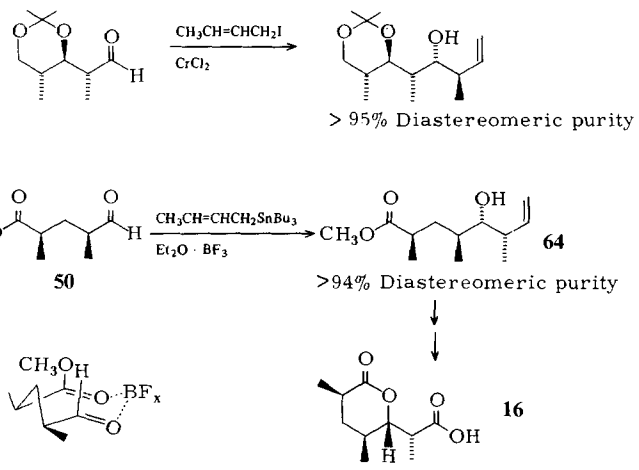


Scheme 10. The configuration of the second newly formed chiral center is not considered.

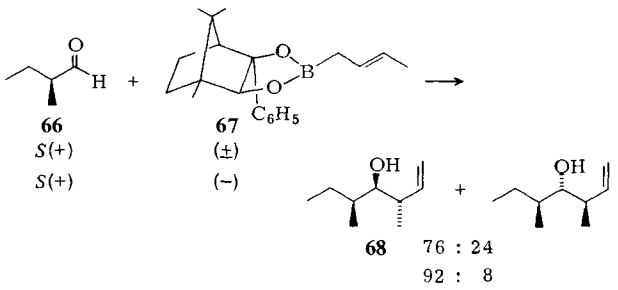
The chiral center in the α-position of the aldehyde causes a 1,2-asymmetric induction. As a result, the two diastereomers are formed in different yields. Of course, reactions leading in high selectivity to only one diastereomer are desirable. The extent of 1,2-asymmetric induction in the addition to α-chiral carbonyl compounds has been examined, in particular, by *Cram et al.*[100]. According to Cram's rules the isomer **62** should be formed preferentially. Compounds **62** and **63** are, therefore, also designated as Cram and *anti*-Cram products, respectively.

The Cram/*anti*-Cram selectivity problem is of course relevant to the addition of crotyl- and allylmetal compounds to α-chiral aldehydes. Examples of surprisingly high diastereoselectivity are found in the syntheses of rifamycin by *Kishi et al.*[89] and the Prelog-Djerassi lactone **16** by *Maruyama et al.*[117].

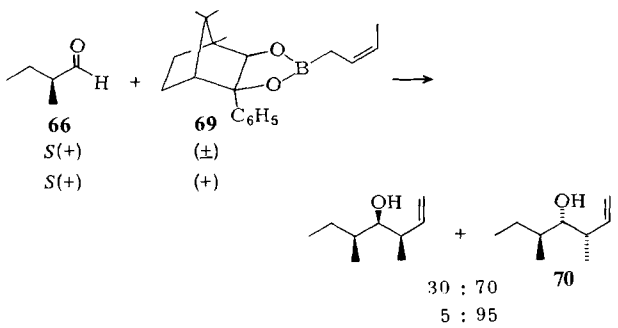
In the last example, the preferred attack at the *re*-side of the aldehyde **50** forming **64** is probably due to complexation (cf. **65**). Unfortunately, the Cram/*anti*-Cram selectivities are often only in the range 2—5 : 1 in the addition of crotylmetal compounds[54-56,69,81,104] and substituted allylmetal compounds[101,102] to α-chiral aldehydes. The reason is that the asymmetric induction is due to only one of the



reaction partners, namely the aldehyde. A higher degree of selectivity is attainable when the two faces of the crotylmetal compounds are made diastereotopic as well. This is possible *e.g.* through a chiral modification of the reagent **26** to give **67**.



A proper combination of the chiralities of aldehyde (+)-**66** and reagent (−)-**67** results in a mutual reinforcement of the individual stereodifferentiations; this "double stereodifferentiation"[6] has proved of value in the aldol addition[8,9,22,103], and could thus be used to improve the selectivity to 92 : 8 in favor of the diastereomer **68**[69]. For comparison, the addition of *rac*-**67** to (+)-**66** gives a selectivity of 76 : 24, because this reaction is only subject to single stereodifferentiation from the aldehyde. Surprisingly, the *anti*-Cram isomer **70** predominated in the addition of the *Z*-crotylboronic acid ester *rac*-**69** to the aldehyde (+)-**66**. In this case, (+)-**69** has the "correct" chirality to increase the selectivity in favor of **70** through double stereodifferentiation.



Similarly, the reaction of **50** with (+)-**69** occurs with a diastereoselectivity of ≥81 : ≤19 thanks to the double

stereodifferentiation[69]. The Prelog-Djerassi lactone **16** was easily obtained from the adduct, although in this case the stereoselectivity was not as high as in the addition of chiral enolates[10,22] to **50**.

6. Conclusion

When an *anti*-adduct such as **13** is desired, of the many possibilities for diastereoselective addition of crotyl residues to aldehydes, the reaction of the *monohapto*-chromium **53** or -titanium compounds **56**—**60** should be the method of choice. In order to obtain the other diastereomer **15**, the use of the crotyltin compound **46** or the *Z*-crotylboronic acid ester **25** is the most advantageous. If alkyl groups other than methyl are desired as appendages at the new CC bond, the requisite tributylstannyl or the chromium(II) derivatives are probably most readily prepared. The diastereoselective positioning of heteroatoms, *e.g.* oxygen, sulfur, or silicon at the branching point, is particularly well achieved using allylboronic acid esters.

It is clear, therefore, that crotylmetal compounds such as **12** or **14** are equal or even superior to the enolate reagents **9** (Scheme 1) with respect to both structural variety and diastereoselectivity in addition reactions to aldehydes (Scheme 2). Another advantage is the high chemoselectivity of the allylboronic acid esters and the allylchromium reagents[54,55], both of which react selectively at the aldehyde function of a ketoaldehyde (cf. **7**→**8**). The chemoselectivity of allylsilicon[66], allyltin[65], and *trihapto*-crotyltitanium[34] reagents is less pronounced, since these react with aldehydes and ketones under comparable conditions. Allylboronic acid esters are also the reagents of choice for asymmetric induction through chiral modification[15,16,69]. However, these have not yet reached the standard set by the enolate reagents using chirally modified enolborinates[8-10].

The work described here originating from our own group is due, in particular, to the initiative and persistence of Dr. H.-J. Zeiß, W. Ladner, and Dr. B. Kemper to whom I express my thanks. Thanks are also due to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for continued support.

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Basic Principles of the CIP-System and Proposals for a Revision

By Vladimir Prelog* and Günter Helmchen

Dedicated to the memory of Robert Sidney Cahn (June 9, 1899—September 15, 1981) and of Sir Christopher (Kelk) Ingold (October 28, 1893—December 8, 1970)

"From Configurational Notation of Stereoisomers to the Conceptual Basis of Stereochemistry" is the title of a lecture [V. Prelog, ACS Symp. Ser. No. 12 (1975) 179] in which the chronologically and alphabetically third member of the CIP-triumvirate discusses the history of the CIP-system. The experience accumulated in the meantime, particularly the efforts to teach computers to use the system as described in 1966 by Cahn, Ingold and Prelog, has shown that certain of its aspects must be more strictly formulated and others modified. Questions dealing with stereoisomers (and stereotopicity), which previously have been treated predominantly in a pragmatic manner, are now discussed in a systematic way.

1. Introduction

The last publication in this journal on this topic appeared in 1966[1]. Although in general the CIP-(*Cahn-Ingold-Prelog*) system has served its purpose well, even for special cases not taken into account sixteen years ago, accumulated experience has since shown that there is a need for revision, or at any rate for a more precise formulation of some of its aspects. Contributory to such experience have been our own work, discussions with other colleagues active in this field, and the work of *Meyer* and *Custer*[4] on adaptation of the CIP-system to computer use. Apart from its contribution to the field of stereoisomerism, the CIP-system has come to serve as the basis for the specification of stereotopicity[5,6] to which it has bequeathed its own shortcomings. This and other aspects unforeseen sixteen years ago have made it necessary now to deal in a systematic way with questions which earlier had been answered on a pragmatic basis only.

One serious constraint is necessary in any kind of revision of the CIP rules: previously assigned descriptors should remain unchanged as far as at all possible and should be altered only for compelling reasons, or in problematic cases to which the system has not yet been applied. To this we would add a second limitation: the need for self-restraint in introducing yet more to the already existing surfeit of new stereochemical terms, many of which could well be replaced by established concepts of elementary geometry. We feel that, particularly for educational reasons, economy in coining new terms should be the order of the day.

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Before going into detail concerning our proposals for revision we would like to reiterate the basic tenets of the CIP-system in order to demonstrate its logical construction and self-consistency, notwithstanding the arbitrary nature (mainly for historical reasons) of some of its conventions. We feel that this is necessary in view of certain, in our view, unjustified criticisms[7,8].

2. Basic Principles of the CIP-System

2.1. Stereomodels

One of the important aims of static stereochemistry is the specification of the geometry and topography of stereoisomers[9]. We define stereoisomers as different molecular species of equal constitution (same atomic makeup and atomic bonding), which are separated by intervening energy barriers[11]. Since for the purpose of the specification of stereoisomers the order of magnitude of these barriers and the physical nature of the bonding, as well as time-dependent properties are immaterial, we assign to molecules rigid stereomodels; geometrical figures, which should contain only the information necessary for that purpose.

The model which is our point of departure is a rigid framework of fixed points connected by straight lines. The points define the spatial arrangement of the atomic nuclei and the lines the chemical bonds.

2.2. Chiral, Helical, and Tripodal Four-Point Figures and their Chirality Sense

For the description of stereomodels one can advantageously use internal ("chemical") coordinates, bond lengths, and bond and torsion angles, since they are invariant towards translation and rotation of the model as a

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whole. Models of nonplanar stereoisomers contain at least one chiral arrangement of four distinguishable points (a chiral three-dimensional simplex) of which two enantiomorphic versions are possible. Since enantiomorphic[13] arrangements are not defined by the absolute values of internal coordinates they have to be specified[15].

As *Möbius*[18] already showed in 1827, this can be expressed by the algebraic sign of the volume of the corresponding chiral tetrahedron as calculated from the coordinates of its specified vertices in a given Cartesian coordinate system[19]. There are, of course, many other equivalent procedures for specification of a chiral four-point figure by an algebraic sign. If we start with internal coordinates it is convenient to use instead of Cartesian coordinates of four points the three bond vectors $\vec{x}$, $\vec{y}$, $\vec{z}$ connecting them. If the bond vectors $\vec{x}$, $\vec{y}$, $\vec{z}$ constitute a right-handed system, then the algebraic sign of the volume of the corresponding tetrahedron in a right-handed Cartesian coordinate system is positive: if they constitute a left-handed system it is negative.

In principle, there are two possible arrangements of three bonds connecting four points: helical and tripodal (Fig. 1). In the helical arrangement the sequence of points

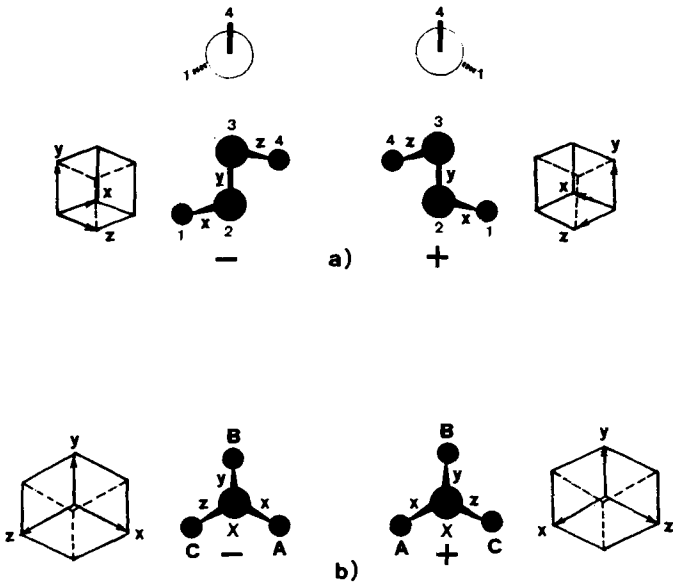


Fig. 1. Fundamental three-dimensional chiral figures (simplices): a) Helical arrangements of four points, their bond vectors and torsion angles. b) Tripodal arrangements of four points and their bond vectors.

can be deduced from the direction of bond vectors as defined by their topological sequence ($1>2>3>4$ or $4>3>2>1$). The bond vector directions are then $\vec{x}=\overrightarrow{12}$, $\vec{y}=\overrightarrow{23}$, $\vec{z}=\overrightarrow{34}$. In the tripodal arrangement the sequence of three topologically equivalent points A, B, and C and the bond vector directions must be defined by a non-topological criterion *i.e.* by conventional rules, for example $A>B>C$ and $\vec{x}=\overrightarrow{XA}$, $\vec{y}=\overrightarrow{XB}$, $\vec{z}=\overrightarrow{XC}$.

In chemistry instead of algebraic signs, expressions such as "right" and "left" or synonymous words and descriptors are used: these, as well as the algebraic signs, signify the *chirality sense* of that arrangement, a useful concept when dealing with stereoisomorphism and stereoisomerism. The chirality sense is unaffected by deformations of the stereomodel; it remains the same provided that the four points do not move into a plane. It is synonymous with the classical concept of "absolute configuration" and at the same time is better defined. Finally, the concept of chirality sense enables one to deal with both tripodal and helical structures within the same general framework. We would like to point out that the distinction between helical and tripodal arrays of four points can serve, according to *Gerlach*[20], as the basis for a rational definition of frequently used concepts, such as conformation and configuration, for which no generally accepted definitions exist[21]. Structures and stereomodels which differ in their tripodal arrangements have different configurations, those which differ in their helical arrangements are of different conformation.

2.3. Two-Dimensional Chirality, Heterotopy

It is possible to apply the concepts of chirality and chirality sense to spaces whose dimension is either less or more than three. In fact, discussion of two-dimensional chirality can lead to a better understanding of three-dimensional stereoisomerism.

The internal coordinates of a planar stereomodel are bond lengths and bond angles. The simplex of two-dimensional space is a three-point figure, the triangle. When this has three distinguishable vertices, it is two-dimensionally chiral, just as the tetrahedron with four distinguishable vertices is three-dimensionally chiral.

The simplest stereomodel containing a two-dimensional chiral triangle is the bipodal arrangement of three atom points (Fig. 2), from which the two topologically equiv-

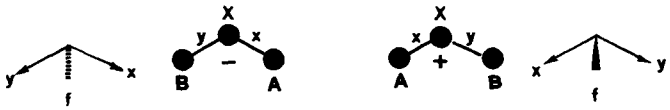


Fig. 2. Two-dimensionally chiral simplex: dipodal arrangements of three points, and their bond vectors.

alent arrangements, A and B, have to be differentiated by conventional rules. In two-dimensional space such an arrangement can exist in two enantiomorphic non-congruent versions which, however, become congruent in three-dimensional space by rotation. Their enantiomorphism is due to the fact that in two-dimensional space they are "orientated". In three-dimensional space their two-dimensional chirality is manifested by the fact that a chiral triangle has two distinguishable faces[22].

In an analogous way to three-dimensional tripodal arrangements it is possible to specify two-dimensional enantiomorphic models or the faces of chiral triangles by the algebraic sign of the area calculated from the Cartesian coordinates of their vertices, or through the algebraic sign of the vector product $\vec{f}=\vec{y}\times\vec{x}$ of the two bond vectors $\vec{x}$ and $\vec{y}$ (Fig. 2).

The plane which contains a two-dimensional chiral simplex divides the three-dimensional space into two distin-

guishable half-spaces, which can be specified by the algebraic sign (or by a corresponding descriptor) of the adjacent face of the chiral triangle. Atoms, ligands, and other objects which are located within such distinguishable half-spaces have been termed heterotopic by *Mislow* and *Raban*[23].

2.4. Factorization of Complex Stereomodels into Stereogenic Units

Non-planar stereomodels with chiral regions containing more than four connected points can be factorized into four-point regions which can be either tripodal or helical. However, factorization down to regions of four directly connected points is performed only in the case of helical arrangements. For historical and practical reasons, stereomodels which contain three-dimensionally chiral tripodal as well as two-dimensionally chiral dipodal regions are subdivided into units containing more than four or three atoms, respectively, which following a suggestion by *McCasland*[24] we term "stereogenic units". It is essential for such a unit to be composed of an achiral core (atom or a skeleton of atoms) with distinguishable ligands, whose constitution-preserving interchange leads to a stereomorphic figure.

2.5. Chirality Elements: Stereogenic Units of the CIP-System

In this paper we wish to restrict ourselves to proposals for revision of the CIP-system concerning stereoisomers with atoms having no more than four ligands. However, subject to appropriate modification, these proposals will also be found applicable to an eventual revision of the rules specifying stereoisomers containing atoms of higher ligancy.

For stereomodels of molecules with at most tetraligant atoms, three types of tetrahedral stereogenic units (three chirality elements) are used in the CIP-system: the chirality center, the chirality plane, the chirality axis, and the analogous pseudoasymmetric units. These we shall discuss and analyze as far as the stage of elementary tripodal and helical regions. Apart from these we shall also consider as stereogenic units planar diastereomorphic arrangements of four ligands of planar tetraligant atoms or double bonds which are commonly described as *cis,trans*-isomers[25].

2.5.1. Chirality Center: The Tetrahedral "Asymmetric Atom"

Among three-dimensional stereomodels with more than four points we shall first discuss the five-point figure shown in Figure 3. This is in fact the model for tetrahedral atoms with four distinguishable ligands, which are of overriding importance in organic stereochemistry. A five-point figure of this type can be converted in four different ways into tripodal four-point figures by omission of one conventionally chosen ligand atom point and its bonds. The chirality sense of each of the four-point figures thus obtained would define unambiguously that of the five-point figure. There is, however, a fifth possibility of mapping such a

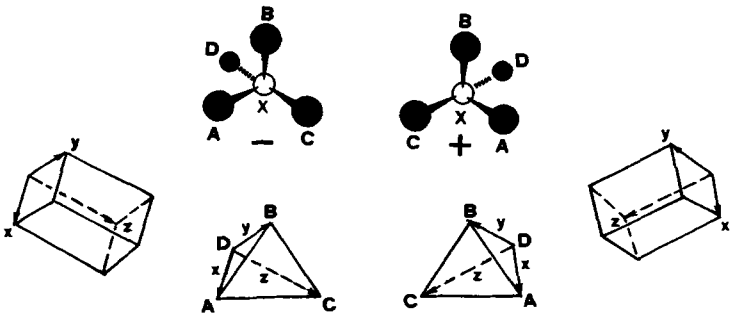


Fig. 3. Chirality center: enantiomorphic tetrahedral "asymmetric" atoms, corresponding T_d-tetrahedra, and their bond vectors.

five-point figure onto a homomorphic complementary four-point simplex. In this, the topologically unique central atom point and its four bonds are omitted, and the remaining four points are placed at the vertices of a regular tetrahedron with point symmetry T_d[26]. The resulting four-point model, unambiguously derived from the original five-point model, is in fact the "asymmetric atom" of *Le Bel* and *van't Hoff*, and at the same time the "chirality center" of the CIP-system.

By such a conversion of a chiral five-point figure into a four-point stereogenic center, considerable simplification of the specification process is achieved. Moreover, the concept of the "asymmetric atom" is so deeply rooted in the mind of the organic chemist that a specification system based on more fundamental tripodal four-point units would have had little chance of acceptance.

In the CIP-system, even a chiral tripodal triligant atom is converted into a tetrahedral one by adding a "phantom" atom. If the directions of the bond vectors are determined in the conventional manner, then the algebraic signs specifying corresponding tripodal and tetrahedral systems are the same. Such a conversion has the advantage of making it possible to specify the chirality sense of both tripodal four-point models of triligant atoms and of tetrahedral five-point models of tetraligant atoms in an analogous manner.

2.5.2. Chirality Plane and Chirality Axis: Their Specification Based on Preferred Helical Regions

To specify the chirality of certain stereoisomers which do not possess centers of chirality (stereoisomeric allenes, atropisomeric biphenyls and *ansa*-compounds) two additional stereogenic units were introduced in 1956: chirality planes and chirality axes.

Figure 4 shows two enantiomorphic five-point figures which are fundamental for representing a chirality plane. In each there is a planar two-dimensionally chiral trigonal atom X, with its proximal atoms or ligands A, B, Y and an additional atom Z connected to Y and lying outside the ABY plane (chirality plane). Such figures can be mapped unambiguously onto four-point simplices. As pointed out in 1972[6] one can omit the planar trigonal atom X and its three bonds and then connect the remaining four atom-points with straight lines. This will lead to the formation of a tetrahedral model of point symmetry C_s with two topologically equivalent vertices which have to be differentiated by conventional rules in order to obtain a tetrahe-

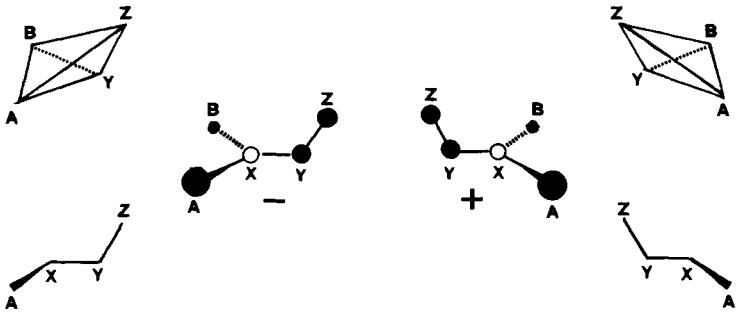


Fig. 4. Chirality plane: enantiomorphic five-point figures, corresponding C_s-tetrahedra, and preferred torsion angles A—X—Y—Z.

dral stereogenic unit, which is then specified in the usual way.

In an analogous manner Figure 5 shows the enantiomorphic figures needed to represent a chirality axis: two nonplanar combinations of planar-trigonal atoms Z_1 and Z_2 with their respective proximal ligating atoms. Such a six-point figure can likewise be mapped unambiguously onto a four-point simplex, a tetrahedron with point symmetry D_{2d}, by omitting atoms Z_1 and Z_2 and their bonds followed by interconnecting the remaining four ligand atom points by straight lines. If the ligand atoms occupying the topologically equivalent positions are distinguishable, the resulting figures are representations of tetrahedral stereogenic units, which again can be specified by an algebraic sign in the same way as the other two chirality elements. The line of intersection of the two planes of the trigonal atoms constitutes an axis, hence this stereogenic unit was termed "chirality axis".

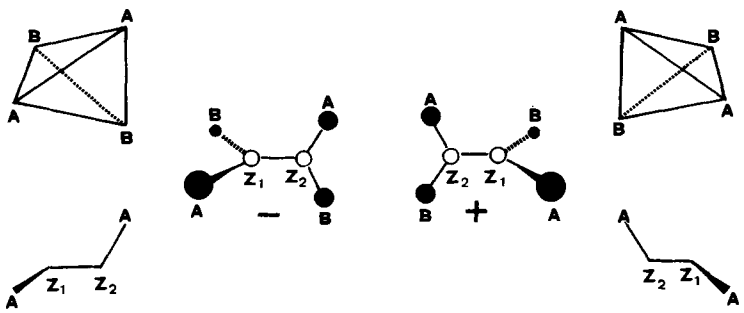


Fig. 5. Chirality axis: enantiomorphic six-point figures, corresponding D_{2d}-tetrahedra, and preferred torsion angles A—Z_1—Z_2—A.

It had previously been recognized[1] that planes and axes of chirality can also be specified by the algebraic sign (or the corresponding descriptor) of the torsion angle of a helical array of four atoms chosen by a conventional rule. We now suggest that this simple and unambiguous method should be applied generally in place of the less convenient specification procedures based on tetrahedral simplices. For chirality planes the preferred sequence of atoms is A—X—Y—Z (Fig. 4), and for chirality axes A—Z_1—Z_2—A (Fig. 5), as already proposed previously. Since stereoisomers with chirality planes and chirality axes are in fact atropisomeric conformers, their specification *via* the algebraic sign of a preferred torsion angle is particularly appropriate (cf. [17]).

Between points X and Y in a chirality plane and points Z_1 and Z_2 in a chirality axis it is possible to insert various linear atom-sequences (*e.g.*, =C=, —C≡C—) which thus do not influence the specification process. An example of practical significance is that of the chiral allenes containing the linear grouping =C=.

The fact that there are molecules with several chirality planes or axes has been mentioned previously[1]. If such stereogenic units are interdependent, then of the possible unambiguous specifications the one chosen should be in accord with *Einstein*'s advice: "Keep it as simple as possible but not simpler than that". A multitude of redundant descriptors[28] will only confuse rather than elucidate. In case of doubt one should clarify the affiliation of a descriptor by giving the systematic numbering of an appropriate atom, as is customary for differentiating several chirality centers or double bonds; and this atom should advantageously be that among those termed Z_1, Z_2 or X or Y, with the lower systematic number.

Among stereomodels with more than six atoms we should briefly mention a seven-point figure comprising a planar trigonal and a tetrahedral atom (Fig. 6). This can be

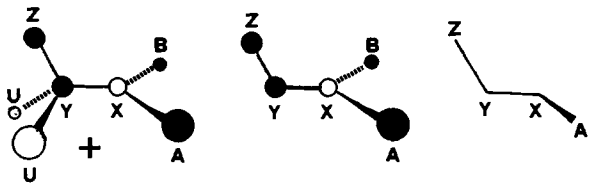


Fig. 6. A seven-point figure, the corresponding chirality plane, and the preferred torsion angle.

unambiguously mapped onto the five-point figure shown in Figure 4, by the choice of one of three topologically equivalent ligands of atom Y or, in other words, it can be treated as a plane of chirality. The choice of the ligand has to be made in accord with criteria derived from the specification of conformations[17].

2.5.3. *"Pseudoasymmetric" Stereogenic Units*

The concept of the stereogenic unit comprises not only the elements of chirality mentioned so far, but also the analogous elements of pseudoasymmetry: pseudoasymmetric centers, planes, and axes. These always exhibit two ligands which differ only in their topography, *i.e.* which are enantiomorphic. In a tetrahedral stereogenic unit such ligands are situated within heterotopic half-spaces; the chirality sense of such enantiomorphic ligands and of the half-spaces can be combined in two geometrically different ways [(+ +, − −) or (+ −, − +)]. This leads to two geometrically different models and to two diastereomers.

Formally, such stereoisomers can be specified analogously to those comprising chirality elements with four

distinguishable ligands. In contrast to the algebraic sign (or corresponding descriptor) of a chirality element, the algebraic sign of a pseudoasymmetric unit obtained in this way is reflection invariant, because diastereoisomerism is based on a geometrical property. Upon reflection, the chirality sense of both enantiomorphic ligands and their halfspaces are reversed; the two inversions cancel each other out.

2.5.4. *The Two-Dimensionally Chiral Triligant Atom. Two-Dimensional Diastereomorphism: "Geometrical" Isomerism*

A planar four-point figure (Fig. 7a), representing the model of a triligant central atom with three distinguishable ligands, can be unambiguously mapped onto a regular triangle in which the central atom and its three bonds have been omitted. This gives the model of the planar "two-dimensional asymmetric atom", analogous to the tetrahedral "asymmetric atom". Previously we showed how one can change the model of a tripodal array into a tetrahedral stereomodel by adding a "phantom" atom: in the same way a bipodal array can be transformed into a trigonal "two-dimensional asymmetric" atom.

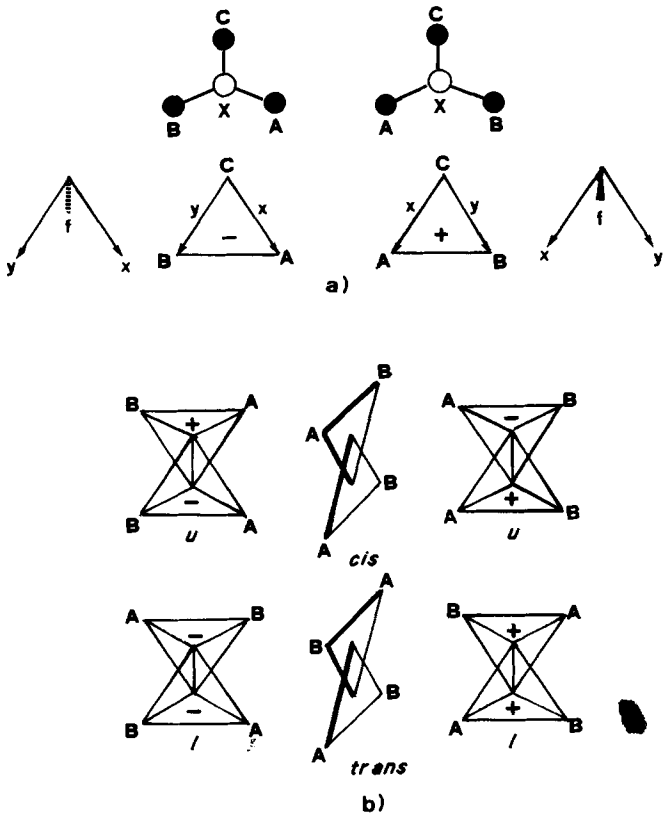


Fig. 7. a) Two-dimensionally enantiomorphic trigonal "atoms" and their bond vectors. b) Two planar diastereomorphic six-point figures composed of two trigonal two-dimensionally chiral atoms; *cis-trans* isomerism.

As indicated in Section 2.3, enantiomorphic "two-dimensional asymmetric atoms" are congruent in three-dimensional space but non-congruent in the plane because of their different "orientations". From two such orientated "two-dimensional asymmetric" atoms two pairs of planar figures can be constructed: one from two differently and one from two equally orientated atoms. Two pairs are diastereomorphic not only in two-dimensional but also in three-dimensional space (Fig. 7b). They are interconvertible by a constitution-preserving interchange of two ligands. A planar combination of two two-dimensional chiral simplices thus represents a stereogenic unit by definition. The two diastereomorphic figures just mentioned are models of *cis-trans* isomers containing planar tetraligant atoms or double bonds.

2.6. Differentiation of Ligands

To establish the chirality sense of a stereogenic unit it is necessary to determine the rank of its ligands by comparing their properties. Since ligands can differ in several types of properties and the rank of ligands must be determined by a single property, this requires a clear-cut hierarchy of relevant properties and an unambiguous prescription for the order in which they are compared. Moreover, the comparison must be performed in a finite number of steps[8].

The properties used in the CIP-system for differentiation of ligands (see Scheme 1) can be divided into material and structural. Material properties are atomic number and (with isotopes) mass number, whereas structural properties include those based on topology (connectedness), geometry, or topography (cf. Section 2.1[9]). Material and topological differences, which in organic chemical usage are termed constitutional differences, are considered first, followed by geometrical differences (either two- or three-dimensional ligand diastereomorphism); topographical differences (ligand enantiomorphism) are treated last. The relative status of the three types of properties is apparent from the sequence (top to bottom) shown in Scheme 1.

constitutional (material and topological)	reflection-invariant
geometrical (diastereomorphic)	
topographical (enantiomorphic)	reflection-variant

Scheme 1. Hierarchical order of ligand properties.

It is essential to examine the relevant properties of ligands in the hierarchical sequence outlined—exhaustively for each type—before proceeding to the next lower rank. This can be formulated also in the following way: equality with respect to a certain type implies equality relative to that of the higher but not lower rank. For example, geometrically equivalent ligands must be equivalent topologically but can be different topographically. The importance of

the precept was recognized only after 1966; nonetheless the Sequence Rules[1] as originally formulated did already follow the correct hierarchical order, a fact that was due to pragmatic recognition of the consequences of not following such an order in a number of cases (see examples *(21)—(23)* in [1]). In spite of this, several cases have since been found where the CIP-system appeared to fail because geometrical and topographic properties had not been properly kept apart. In fact, differentiation is always feasible so long as one keeps in mind that differences in topography are based on the reflection-variant enantiomorphism of two ligands, *i.e.* on their chirality sense, whereas all other properties, geometrical and constitutional, are reflection-invariant. Here it is advisable to point out that a relevant property of a particular ligand used for specification must not be based on its relationship to the stereogenic unit to be specified. This caveat has been discussed in [1] with special reference to the configuration of the inositols. Finally it should be pointed out that two ligands which are ordinarily equivalent but heterotopic, and thus chemically and physically distinguishable, are of the same rank order: their heterotopy alone is not a sufficient distinction criterion for determining their order of precedence.

3. Hierarchical Digraphs

So far we have consistently used the term ligand, without defining it. Its meaning is quite clear in the case of monodentate ligands. On the other hand, for polydentate and cyclic "ligands", especially as parts of polycyclic structures, the term appears to lose its clear connotation. This can be rectified by converting the polydentate and cyclic ligands into equivalent acyclic structures: their hierarchical digraphs.

The hierarchical digraph of the whole stereogenic unit is a directed chromatic acyclic graph, a "tree-graph" representing the connectedness (topology) and make-up of atoms: its edges, originating from the root of the tree-graph—the core of the stereogenic unit—point towards the branch ends.

3.1. Hierarchical Digraphs of Acyclic Molecules

The non-directed graph of an acyclic molecule is obtained from its constitutional formula by addition of duplicate and phantom atoms. The digraph of a stereogenic unit within this molecule is then obtained by assigning directions to the edges, starting from the core and pointing towards the branch ends (Fig. 8). Frequently it is not only sufficient but also advantageous, especially with larger molecules, to use simplified instead of complete hierarchical digraphs. In these simplified versions the nonrelevant hydrogen and phantom atoms are omitted and carbon atoms replaced by their systematic numbering. In developing such a graph one need only proceed to the extent of determining the rank order of all ligands. The spatial arrangement of the proximal atoms of the core of the tetrahedral stereogenic unit is shown advantageously in such simplified digraphs by using Fischer projections.

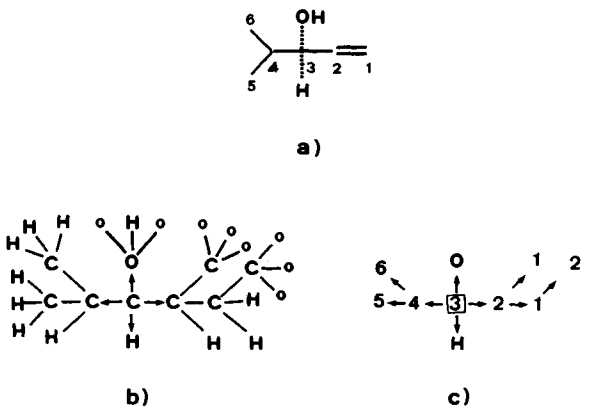


Fig. 8. a) A constitutional formula in which the configuration of stereogenic atom C-3 is represented by Fischer projection. b) Complete hierarchical digraph of a. c) Simplified hierarchical digraph of a.

In the case of an acyclic molecule containing several stereogenic units the hierarchical digraphs of all these units are derived from one and the same non-directed molecular graph (Fig. 9).

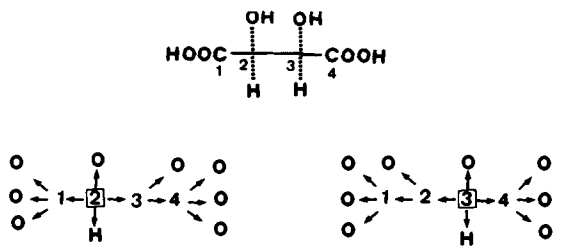


Fig. 9. An acyclic molecule: derivation of the hierarchical digraphs of both stereogenic atoms C-2 and C-3 from the same molecular non-directed graph.

3.2. Hierarchical Digraphs of Cyclic Molecules

In order to transform the constitutional formula of a cyclic molecule into an acyclic "tree-graph" all rings have to be opened in such a way that the resulting acyclic graph contains all the necessary but no redundant information. This procedure has so far not been properly described, and we shall do so in the following sections.

3.2.1. Stereogenic Units with Polydentate Ligands

In order to obtain the acyclic digraph of a stereogenic unit the n-dentate ligand is transformed into n monodentate ligands, by leaving intact in each case one bond with the core and breaking the remaining n − 1 bonds. At each end of n branches thus obtained a duplicate atom of the core is attached (as in the case of broken multiple bonds) (Fig. 10).

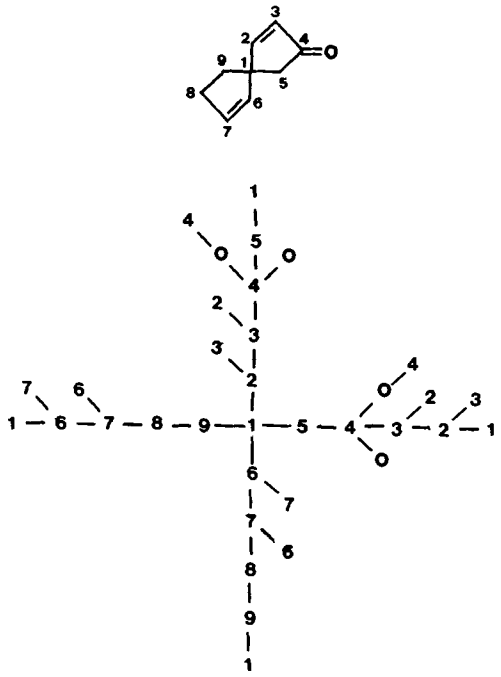


Fig. 10. Hierarchical digraph of a stereogenic atom with two bidentate ligands.

3.2.2. *Stereogenic Units with Ligands Containing Rings*

In ligands of a stereogenic unit containing rings these are opened twice after the first ring atom encountered from the core: one bond remains intact and the other is broken; a duplicate of the first encountered ring-atom is attached at the end of the two branches thus obtained (Fig. 11). If the first-encountered ring atom of the ligand turns

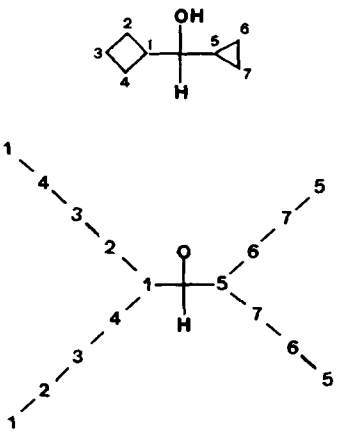


Fig. 11. Hierarchical digraph of a stereogenic atom with two cyclic (three- and four-membered) ligands.

out to be the quaternary common atom of a bicyclic system, one of the three ring bonds is kept intact and the other two are broken. Three branches of the tree graph, which are provided at their ends with requisite duplicate atoms, are therefore produced (Fig. 12).

A characteristic difference between hierarchical digraphs of stereogenic units in acyclic and cyclic molecules is that in the former the non-directed graph is the same, as

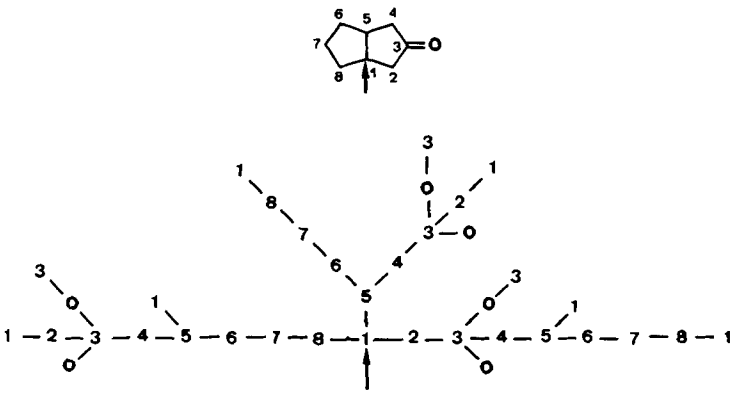


Fig. 12. Hierarchical digraph of a ligand which includes branching due to a bicyclic ring system.

mentioned previously, whereas the digraph of the latter may be derived from the same or from a different non-directed graph, depending on the position of the stereogenic units relative to the ring (see Fig. 13).

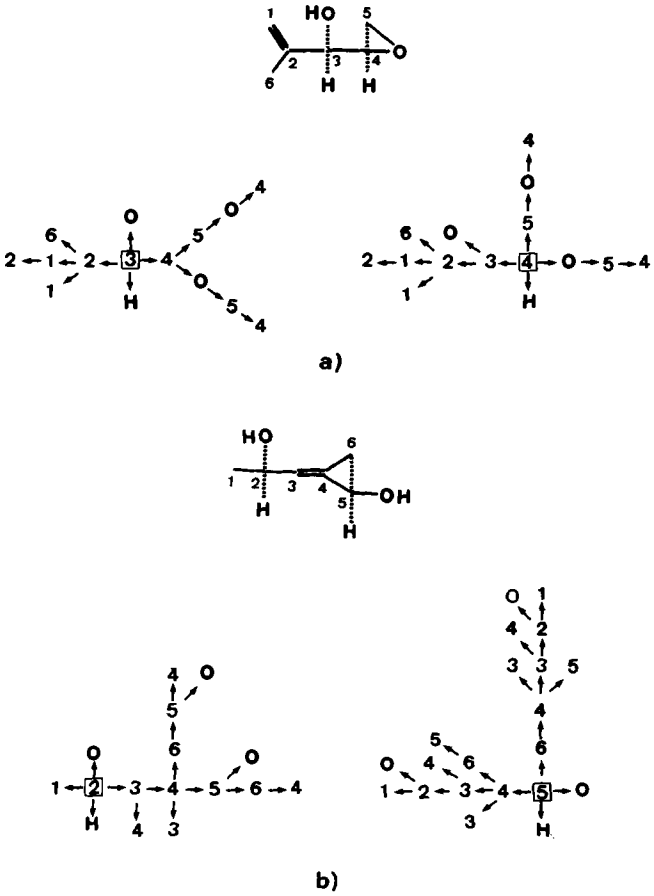


Fig. 13. Hierarchical digraphs of two cyclic molecules with two stereogenic atoms each: a) both digraphs derivable from the same molecular non-directed graph, b) each digraph requiring its own molecular non-directed graph.

3.3. Examination of Hierarchical Digraphs. The Precedence of Atoms as a Result of their Topology

To establish the order of precedence of ligands, their atoms are rearranged in such a way that their rank is ap-

parent both from their topological distance (number of bonds), from the core of the stereogenic unit, as well as from their evaluation by the sequence rules.

Atoms of equal topological distance can be said to lie in the same sphere. Atoms occupying the n-th sphere have precedence over those in the (n + 1)th sphere.

The ranking of each atom within an n-th sphere depends in the first place on the rank of the atom within the (n − 1)th sphere to which it is bonded, and only then on its rank according to the sequence rules. The first sphere is occupied by the proximal atoms p, p′ (Fig. 14). Those in the second sphere are numbered 1,2,3,..., and those in the

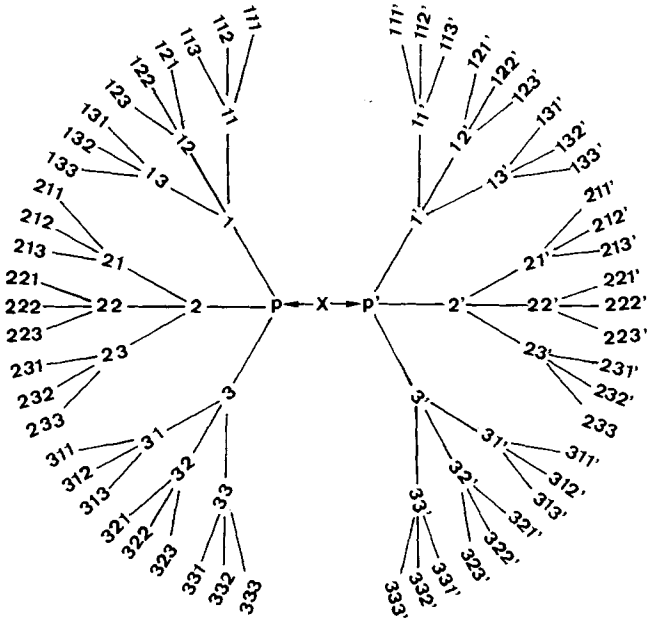


Fig. 14. Rank order of two ligands with proximal atoms p and p′.

third sphere 11, 12, 13, 21, 22, 23 ... *etc.*; the smaller the number, the higher the relative ranking.

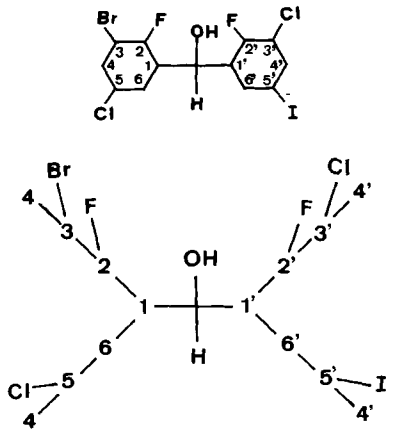


Fig. 15. Illustration of the precept that a branch rank, once determined, has subsequent priority: to determine order of sequence of both cyclohexyl groups the rank order 3-Br > 3′-Cl is used, and not 5′-I > 5-Cl because the former atom-pair is attached to branches of higher rank due to 2-F and 2-F′, respectively.

Those atoms in the n-th sphere which are of equal rank with respect to those in the (n − 1)th sphere to which they are bonded are graded by means of the sequence rules—and these are applied exhaustively in turn: first the entire hierarchical graph is examined by sequence rule 1. If a clear precedence over other ligands can be established, the examination of that particular ligand is concluded. If ligands remain whose rank is not provided by sequence rule 1, then one uses sequence rule 2, once again exhaustively, and so forth. While this procedure is in accordance with precepts published earlier[1] it now makes clear, we hope, that a rank established for a sphere nearer to the core remains valid with respect to atoms in more distant spheres (Fig. 15).

4. Descriptors

In principle, one could specify stereoisomers by the algebraic sign of their stereogenic units as shown in Figures 1 to 5, wherein vector directions are defined as proceeding from points of lower to those of higher precedence.

There are, however, good reasons for using letters (descriptors) instead of algebraic signs for such specification: 1) (+) and (−) have for long been employed to signify the direction of rotation of polarized light of enantiomers, 2) use of these signs does not clearly establish whether they are reflection-variant or -invariant (cf. Section 2.5.4), 3) use of a multitude of algebraic signs is also not conductive to oral or written transmission of information.

Scheme 2 gives a complete summary of descriptors employed in the revised CIP-system, wherein reflection-variant descriptors are marked by capital and -invariant descriptors by lowercase letters.

The descriptors are:

Re,Si[a)b)]; *re,si*[a)b)]; *R,S*; *r,s*[c)]; *P,M*[d)]; *p,m*[e)]. Abbreviations for descriptor pairs: *lk, Lk, l* for like, *ul, Ul, u* for unlike. *ReRe, SiSi=lk*[f)]; *ReSi=ul*[f)]; *reRe, siSi=Lk*[g)]; *reSi, siRe=Ul*[g)]; *RR, SS, MM, PP, RM, SP=l*; *RS, MP, RP, SM=u*.

a) *re, si* have been suggested by *Hanson*[5] for specifying the lateral faces of planar chiral trigonal atoms. No suggestions were put forward for differentiating between reflection-invariant and -variant faces.

b) We have used *Re, Si, re,* and *si*[6] to specify two-dimensional stereogenic units and heterotopic half-spaces; here, reflection-variant units were denoted by *Re, Si,* and -invariant units by *re, si.*

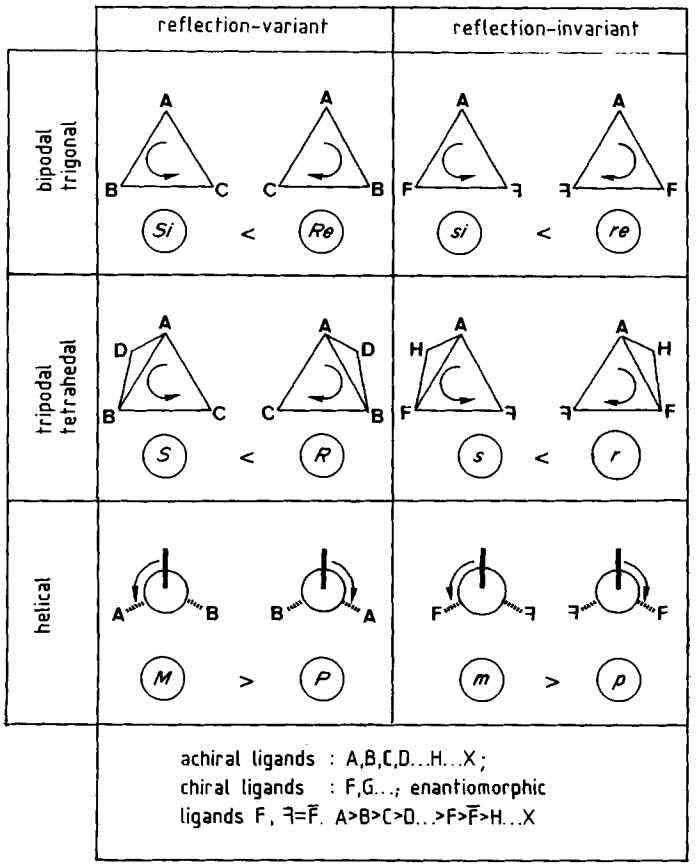
c) *R, S, r,* and *s* were first introduced in [2].

d) *P* and *M* were suggested in [1] and are based on a convention put forward in [17].

e) *p* and *m* are suggested in this paper as symbols for the specification of reflection-invariant "pseudo-asymmetric axes" and "pseudo-asymmetric planes".

f) It might be possible to specify *cis-trans* diastereomers of compounds containing planar tetraligant atoms or double bonds by use of descriptor pairs *ReRe, SiSi=lk* or *ReSi, SiRe=ul,* respectively. However, these offer no advantages over the more graphic *seqcis=Z* or *seqtrans=E* usually employed. On the other hand, the expressions *lk* and *ul* do appear to be particularly suitable

for specifying the steric course of asymmetric syntheses involving reactions between planar triligant atom centers, a suggestion which is dealt with in greater detail elsewhere[29].



Scheme 2. Descriptors of stereogenic units.

g) For the sake of consistency one can use the reflection-variant terms *Lk* and *Ul* for the descriptor pairs *reRe*, *siSi*, and *reSi*, *siRe* for the specification of "geometrically enantiomorphic" stereoisomers (see Section 6.4).

Further to what was said earlier about the convention of vector directions one could equate descriptors *P*, *p* with the algebraic sign +, and *M*, *m* with the sign −. However, for historical reasons *R*, *r*, *Re*, *re* are equivalent to −, and *S*, *s*, *Si*, *si* to +: in 1956 the symbols *R*, *S*, *r*, and *s* were chosen so that most D-sugars and L-amino acids would be allocated descriptors *R* and *S*, respectively.

In cases where stereomodels contain elements of symmetry it may be advisable to subject their descriptors to a test of symmetry consistency. Stereogenic units denoted by reflection-variant terms *R* or *S* can never lie in a symmetry plane. The latter can only accommodate units with reflection-invariant descriptors *r* or *s*. No tetrahedral stereogenic unit should ever coincide with a center of inversion. If the stereomodel contains a plane of symmetry or a center of inversion, every stereogenic unit in that model which can be specified by a reflection-variant descriptor *R* should be accompanied by another enantiomorphic unit specifiable by descriptor *S* and *vice versa*.

A reflection-variant stereogenic atom can conceivably be situated on a two-fold or three-fold axis of rotation. Such relatively rare cases will be discussed, with appropriate examples, in Section 6.3. It is clear that in a stereomodel every n-fold axis of rotation requires at least n stereogenic units having equal descriptors which lie outside this axis.

Here the difference between hierarchical digraphs of cyclic and acyclic molecules should once again be emphasized. With the latter, in which all digraphs are derived from the same nondirected graph, the descriptors of all stereogenic atoms present are definitive—this is not the case with cyclic molecules. Whenever, for the sake of discussion, it is necessary to use such auxiliary descriptors we shall differentiate between these and the definitive descriptors by marking the former with the subscript o.

5. Sequence Rules

5.1. Sequence and Assignment Rules 1966

The Sequence Rules (standard sub-rules) were formulated in 1966 as follows[1]:

(0) Nearer end of axis or side of plane precedes further
(1) Higher atomic number precedes lower
(2) Higher atomic mass number precedes lower
(3) *Seqcis* precedes *seqtrans*
(4) Like pair *R,R* or *S,S* precedes unlike pair *R,S* or *S,R*; and *M,M* or *P,P* precedes *M,P* or *P,M*; and *R,M* or *S,P* precedes *R,P* or *S,M*; and *M,R* or *P,S* precedes *M,S* or *P,R*; also *r* precedes *s*.
(5) *R* precedes *S*; and *M* precedes *P*.

If it is possible to denote the order of precedence of the four ligands a > b > c > d present in a tetrahedral array by application of the Sequence Rules, then stereogenic units are assigned descriptors according to the "chirality rule":

> Among ligands of highest precedence the path of their sequence is followed from the preferred side of the model, that is, the side remote from the group of lowest precedence, and, depending on whether the path turns to right or left, the chirality unit will be assigned the chiral label *R* or *S*, or, if pseudoasymmetric, *r* or *s*.

With a helical array the "helicity rule" applies:

> Depending on whether the identified helix is left- or right-handed, it is designated "minus" and marked *M*, or "plus" and marked *P*.

Although both assignment rules can each be expressed in different ways[30] there is no reason for changing the original versions, which have found their way into elementary textbooks. It might be worth pointing out, however, that they are exchangeable. After having determined the rank

of proximal atoms a>b>c>d, one can determine and specify the stereogenic unit as a right or left helix according to the helicity rule. Alternatively one could construct a tetrahedron from four helically arranged points 1—2—3—4 and specify it according to the chirality rule. Between the descriptors thus obtained the following simple relationships apply: $P \leftrightarrow R$; $M \leftrightarrow S$; $p \leftrightarrow r$; and $m \leftrightarrow s$ (Fig. 16).

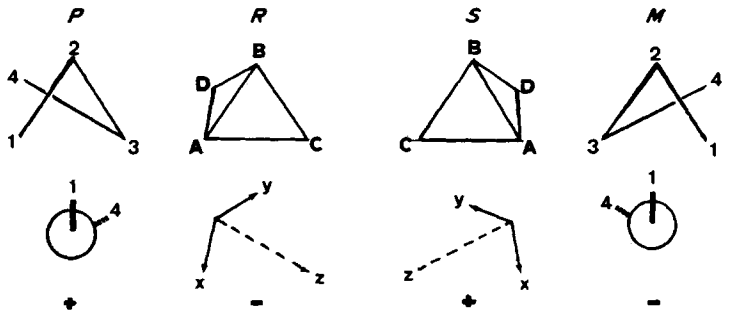


Fig. 16. Equivalent assignments of descriptors by the chirality and by the helicity rule.

5.2. Sequence Rules 1 and 2

In the majority of cases the relative rank of ligands is established on the basis of material differences, *i.e.* by application of rules 1 and 2. These constitute the solid basis on which the CIP system rests and there is no reason for revising them.

5.3. Revision of Sequence Rule 3

In contrast there is a need, in view of more recent developments, for revision of rule 3, dealing as it does with certain of the geometrical differences of ligands. The following will differentiate between ligands which differ in *cis-trans* isomerism due to planar tetraligant atoms or double bonds, and ligands which differ in *cis-trans* isomerism in rings.

5.3.1. cis-trans Isomers Associated with Double Bonds

When two ligands, materially and topologically identical, differ in their geometry at double bonds, rule 3, as applied up till now, has assigned to first encountered double bonds descriptors *seqcis* = *Z* or *seqtrans* = *E*, respectively, followed by establishing precedence through the precept *seqcis* > *seqtrans*. When this rule was put forward, molecules in which assignment of *seqcis* and *seqtrans* is not possible, even though their stereogenic units contain ligands with double bonds differing in *cis-trans* isomerism, were unknown. A simple example is that shown in Figure 17. We therefore suggest the following minor modification of rule 3 in order to specify cases of this type: When two ligands (indistinguishable by rules 1 and 2) differ by one having the atom or the atom-group of the higher rank in a *cis*-position to the core of the stereogenic unit, and the other in a *trans*-position, then the former has precedence over the latter. The original precept in its abbreviated form, *cis* > *trans*, is still valid, but now these terms apply to the location of an atom or atom group of higher rank in relation to the core of a stereogenic unit, rather than to the configuration the double bonds themselves. The way this revised rule applies in the case of Figure 17 is shown by the adjacent hierarchical graph.

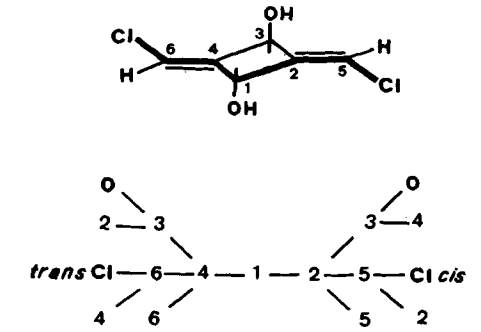


Fig. 17. Stereogenic atoms C-1 and C-3 with geometrically distinguishable unsaturated ligands which cannot be specified using *seqcis* or *seqtrans*, respectively.

Figure 18 should serve to demonstrate that if the modified rule 3 is used in cases where double bonds could be specified alternatively by *seqcis* or *seqtrans*, it would lead

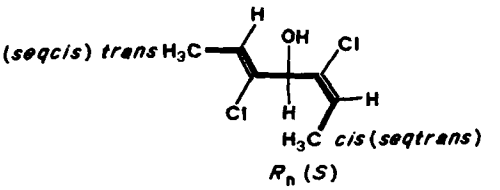


Fig. 18. A stereogenic atom with two geometrically different unsaturated ligands, whose specification by the previous and by the revised rule 3 gives different descriptors (*S* and R_n, respectively).

to a situation in which the previous and the modified rules lead to different descriptors. Hence, even though cases of molecules with stereogenic units whose ligands differ as a result of double bond isomerism are rare[31], and have not hitherto been specified using the CIP-system, we would suggest adding the subscript n (for new) for all descriptors assigned by the modified rule 3.

5.3.2. cis-trans Isomerism in Ring Compounds

Here it is necessary to introduce a substantial change. In principle, *cis-trans* isomerism in ring compounds is three-dimensional diastereomerism. The stereomodels of such diastereoisomers should reveal ligands with at least one pair of three-dimensional stereogenic units specifiable by descriptors such as *R, S etc.* The geometrical differences should be specifiable by either an unlike or like pair of descriptors, respectively. In other words, this type of diastereoisomerism ought to be specified using rule 4 as in the case of analogous acyclic molecules and not rule 3.

Up to now it has frequently been possible to determine the rank of ligands by either rule 3 or rule 4. Any ambiguity had been forestalled by the requirement that each rule had to be applied exhaustively before proceeding to the next one. Nonetheless it seems unreasonable to use two overlapping rules for one and the same type of three-dimensional diastereoisomerism, while at the same time using rule 3 to specify both two- and three-dimensional diastereoisomerism.

Apart from a point of principle there are good practical reasons for modifying rule 3. In the case of multi-membered, polycyclic, or *spiro* ring systems it is often not at all easy to ascertain (even using a computer) which ligands belonging to distant stereogenic atoms are in a *cis*- or a *trans*-position to each other; a point which is especially pertinent when one tries to find an answer to this question on the basis of structural coordinates determined by X-ray analysis.

Unfortunately, and unavoidably, there are cases where descriptors assigned to stereogenic units by the new rule may differ from those established by rule 3 in its original form: to forestall misunderstanding, such descriptors of the "new" type should receive the subscript n.

5.4. Sequence Rule 4

Whereas the actual wording of this rule remains practically unchanged, in view of its applicability to the specification of *cis-trans* isomerism in cyclic molecules its general scope has been considerably extended. Hence it may be necessary to spell out more accurately how one should use it to arrive at an unambiguous specification.

Before applying rule 4 it is useful to derive from the first hierarchical digraph a second one, in which stereogenic centers (or generally units) which had initially been specified using rules 1 to 3 are now replaced by descriptors *R* and *S* (or *M* and *P*) (cf. Fig. 19). One now systematically examines pairs of ligands containing two or more stereogenic units for geometrical differences arising from various alternative combinations of their descriptors. The comparison of such descriptor pairs should proceed in such a way that all relevant but no redundant information is used. This can be achieved by the following procedure based on general CIP principles: Before pairing, the descriptor chosen as first is that highest in rank according to rules 1 to 3. One now forms the descriptor pairs by pairing the one chosen as first in each ligand with one of the (n − 1) remaining descriptors in the order prescribed by the scheme shown in Figure 14. This is then followed by comparing corresponding pairs in both ligands. As soon as a difference is found, rule 4 is used in order to establish the sequence of ligands. The whole procedure is illustrated by examples in Figure 19a—c. In a) the "first" descriptor is the one found in a topologically preferred location, in b) it is the one seen in the highest ranked branch of the hierarchical digraph, and in c) it is the descriptor that occurs twice in the highest ranked triad. The descriptor thus established as first is now paired with other descriptors in the sequence of their order numbers (11, 21, 31, 111, 211 *etc.*), and the descriptor pairs thus formed are in turn evaluated as like (*l*) or unlike (*u*). The first different pair determines the sequence of these ligands.

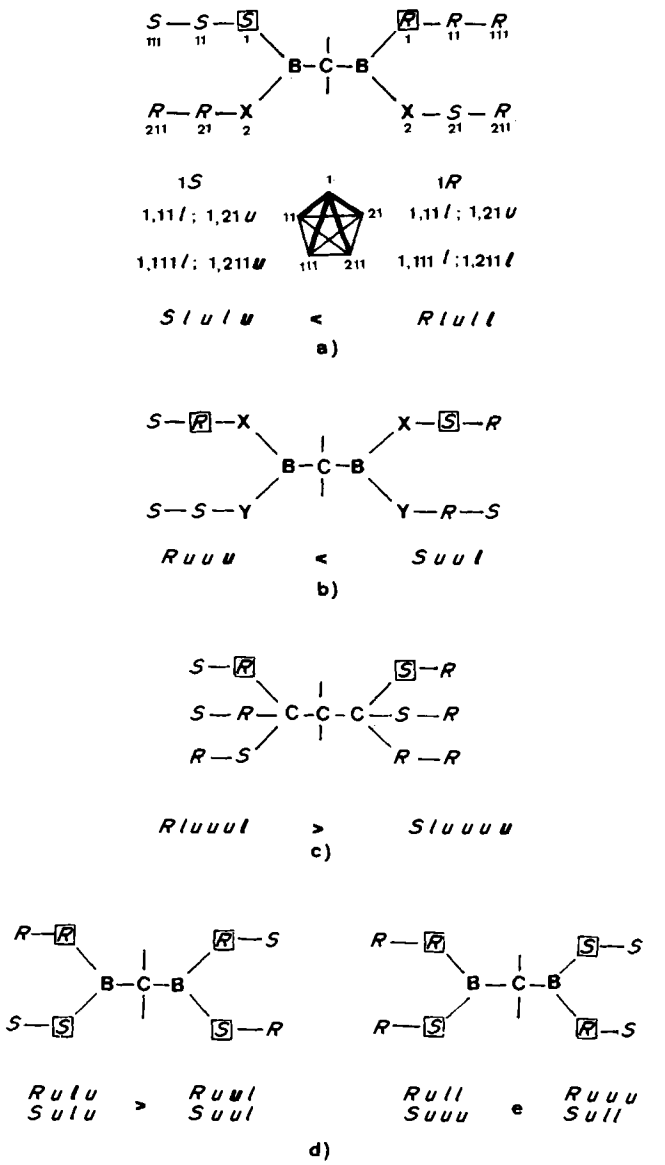


Fig. 19. a) b) c) d) Descriptor assignment in stereogenic atoms whose ligands contain different descriptor pairs.

The rationale of this procedure can be stated as follows: A complete graph whose n vertices represent the descriptors and whose edges represent the n(n − 1)/2 descriptor pairs can be unequivocally mapped onto a spanning tree-graph whose root is the first descriptor. The (n − 1) edges of this spanning tree-graph, shown in Figure 19a as bold lines, contain all the relevant descriptor pairs.

A special case is that of ligands containing enantiomorphic stereogenic units and consequently inverse descriptor pairs in positions of highest rank. Here one forms all relevant descriptor pairs using both the *R*- as well as the *S*-descriptor, after which one compares all pairs situated at the same rank level (Fig. 19d). The highest-ranked difference is then used for establishing sequence. Had only one of the two enantiomorphic ones (*e.g.*, *R*) been used as first de-

scriptor, this would have led to the evaluation of enantiomorphic ligands as geometrically different.

Figure 20 shows the specification of the six stereogenic atoms in (+)-inositol, as an example of sequence determination on the basis of differences between descriptor pairs in a cyclic molecule. The procedure is shown in detail for carbons C-1 and C-2 with the aid of their hierarchical digraphs; the other four atoms can be specified in the same manner. As in the case of acyclic compounds one uses the first-encountered different descriptor pairs in order to evaluate the two branches of the bidentate ligand using rule 4.

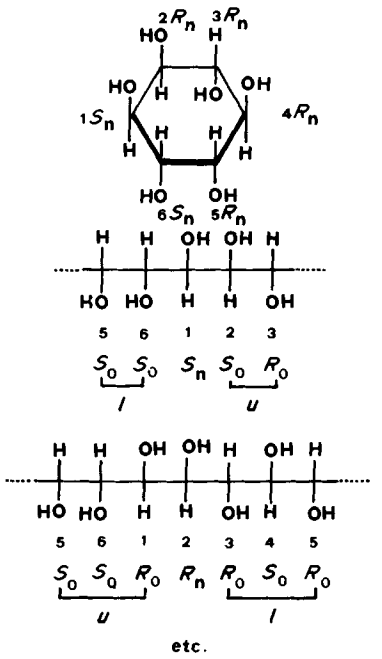


Fig. 20. Descriptor assignment of stereogenic atoms in (+)-inositol.

5.5. Sequence Rule 5

Here, too, the wording of this rule remains unchanged but a few further remarks clarifying its use are necessary.

After having failed to discover any geometrical differences between ligand pairs pertaining to stereogenic units containing descriptors, one proceeds to compare corresponding descriptors in two ligands. If they are inverse, then one uses those of the highest rank for determining sequence.

A pair of enantiomorphic ligands together with two other ligands which are not enantiomorphic together constitute a "pseudoasymmetric" stereogenic unit, which is specified according to rule 5 using reflection-invariant descriptors *r* or *s*.

It should be noted that a stereogenic unit containing two different pairs of enantiomorphic ligands (cf. [32]) is not pseudoasymmetric, but is a chirality element which has to be specified by the reflection-variant descriptors *R* or *S*.

A special case is that of stereogenic units with ligands, whose sole difference is that they contain two different "pseudoasymmetric" stereogenic atoms. The CIP-system recognizes such chirality elements only after all the other stereogenic atoms have been specified by applying rules 1 to 5 (Fig. 21a). The subrule of rule 4, *r* precedes *s*, can thus be applied only after rule 5 has been used to determine descriptors *r* or *s*, respectively. In order to keep to our precept that each rule be employed exhaustively before proceeding to the next one, we suggest that this subrule ($r > s$), even though based on a geometrical difference, become a second part of rule 5.

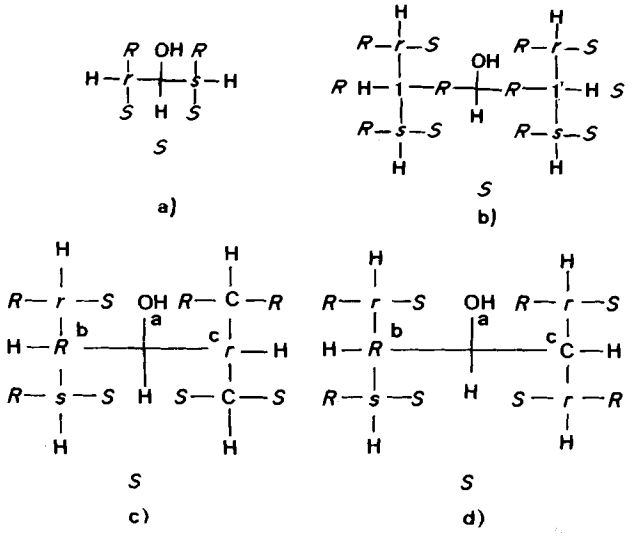


Fig. 21. Graphs with descriptors assigned according to rule 5. The descriptor for the central stereogenic atom in case b) can be assigned only by subsequent reapplication of rule 4 ($l > u$).

It is thus not difficult to envisage structures such as that shown in Figure 21b, in which we meet with the following situation: topological differences engender geometrical differences, which in turn lead to new topological differences. It appears, however, that such compounds have not yet been prepared.

Stereogenic units are conceivable[4b] which contain constitutionally equivalent ligands, differing only in that one of them comprises a chiral and the other a pseudoasymmetric stereogenic unit (Fig. 21c). A ligand with a chiral or pseudoasymmetric stereogenic unit could also be juxtaposed to a constitionally equivalent ligand without the corresponding stereogenic unit (Fig. 21d). In such cases we propose that the chiral stereogenic unit should preceed the pseudoasymmetric one, and the ligands with a chiral or pseudoasymmetric unit should preceed the one without a corresponding stereogenic unit.

5.6. Summary of Revised Sequence Rules

If, as we have recommended, specification of chirality planes and chirality axes is carried out on the basis of preferred helical domains, rule 0 becomes superfluous. Rules 1 and 2 and their application remain unchanged. Rule 3 should henceforth be restricted to ligands which differ in *cis-trans* isomerism of planar tetraligant atoms or double bonds. It should then read as follows: When two ligands differ only in that one has an atom or atom-group of higher rank in a *cis*-, and the other in a *trans*-position to the core of a stereogenic unit, then preference is given to the former.

Revised rule 4 is as follows: When two ligands have different descriptor pairs, then the one with the first-chosen

like descriptor-pair has priority over one with a corresponding unlike descriptor-pair. Like descriptor-pairs are: *RR, SS, RRe, SSi, ReRe, SiSi, MM,* and *PP,* and also by corollary *RM, SP, ReM,* and *SiP.* Unlike pairs are: *RS, ReSi, SRe, ReSi, MP*; and by corollary *RP, SM, ReP,* and *SiM.* The rule stating that a ligand with descriptor *r* has preference over one with descriptor *s* is used as rule 5b, since it will only be used following rule 5a.

Rule 5a reads exactly as the original rule 5: A ligand with descriptor *R* or *M* has priority over its enantiomorph with descriptor *S* or *P.*

6. Parerga and Paralipomena

In the preceding sections we have endeavoured to describe the revised CIP-system in concise form, and to this end we have used only simple and lucid examples to illustrate our arguments. The purpose of this section is to show that the revised system also lends itself to the treatment of more complicated cases, in particular those which various workers in this field have considered unspecifiable.

6.1. The "Finiteness" of the Specification Process

In 1966[11] a statement, supported by two examples, was published to the effect that examination using the Sequence Rules must be terminated when the specifiable chirality center has been reached. In spite of this *Schubert* and *Ugi* stated in 1979 with reference to the molecule shown in Figure 22[8] that "no matter how many iteration steps are performed it is impossible to put the ligands into order. Here the CIP-Sequence Rule fails". They gave another four examples where, in their view, ligands could not be put in sequence and came to the devastating conclusion that the CIP-system "is fundamentally incapable of ordering ligands".

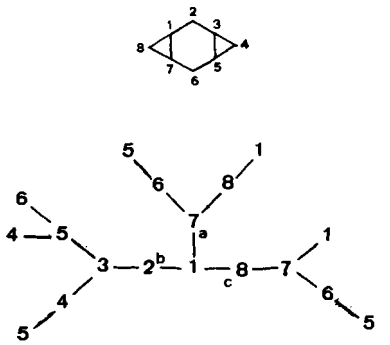


Fig. 22. Hierarchical digraph of C-1 in tricyclo-[5,1,0,$0^{3,5}$]-octane

The hierarchical digraphs of two of the structures used as a negative example (Figs. 22 and 23) demonstrate that this conclusion is completely unwarranted; and the remaining three structures quoted by them can be specified in an analogous manner.

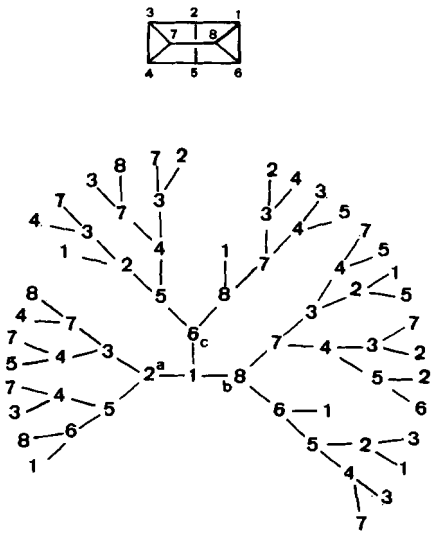


Fig. 23. Hierarchical digraph of C-1 in cuneane.

6.2. Compounds with Hitherto Unspecifiable Stereogenic Atoms

6.2.1. Achiral Cyclic Stereoisomers

A systematic utilization of hierarchical digraphs of cyclic compounds makes it possible to specify "pseudoasymmetric" stereogenic units, which up to now required the use of the *cis-* and *trans*-descriptors. Well-known examples are the stereogenic atoms in 1,3-disubstituted cyclobutanes, in *cis-* and in *trans*-decalin, in all-*cis-* and in all-*trans*-inositols, and in many of their homologues and analogues.

For example, let us consider stereogenic atoms C-1 and C-2 in *cis*-1,3-cyclobutanediol (Fig. 24), which the unre-

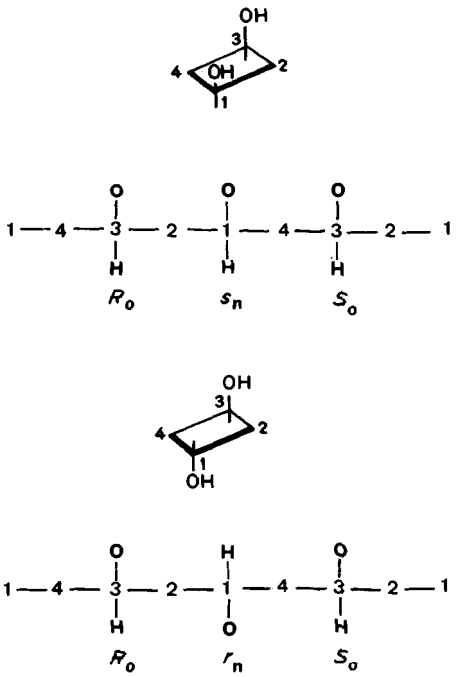


Fig. 24. Hierarchical digraphs of C-1 in diastereomeric cyclobutane-1,3-diols.

vised CIP-system could not specify. In the hierarchical digraph of C-1 we now see that C-3 is a specifiable stereogenic atom in both of the branches corresponding to the ring. In the left branch it is assigned descriptor R_0 and in the right descriptor S_0. Hence C-1 is a pseudoasymmetric

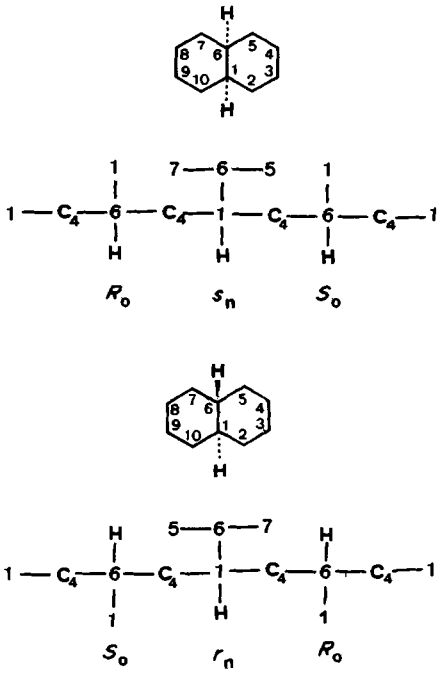


Fig. 25. Hierarchical digraphs of C-1 in diastereomeric decalins.

atom, which by rule 5 is specified by descriptor *s*. The fact that C-3 has different descriptors in each branch demonstrates that this atom is topographically different (enantiomorphic) with respect to C-1. These C-3 descriptors are auxiliaries which do not appear in the final specification. The definitive descriptor of C-3 has to be ascertained by examining its own hierarchical digraph; and this shows that for this atom, too, the descriptor is *s*, in accord with the C_2 point symmetry of the molecule as a whole. By the same procedure one obtains descriptors 1*r*, 3*r* for *trans*-1,3-cyclobutanediol (Fig. 24), 1*s*, 6*s* for *cis*-decalin 1*r*, 6*r* for *trans*-decalin (Fig. 25), and 1*r*, 2*r*, 3*r*, 4*r*, 5*r*, 6*r* for all-*trans*-inositol (Fig. 26).

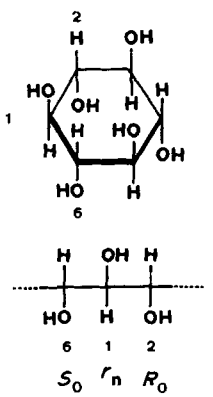


Fig. 26. Hierarchical digraph of C-1 in all-*trans*-inositol.

6.2.2. *2,6-Adamantanediol*

In this molecule we find two stereogenic atoms which until now could not be specified. This particular example shows how one can establish the rank of ligands in the case of a highly symmetrical (T_d) polycyclic framework.

Since obviously O > C, C > H, what one has to tackle is the problem of the proximal ligand atom pairs (C-1, C-3)

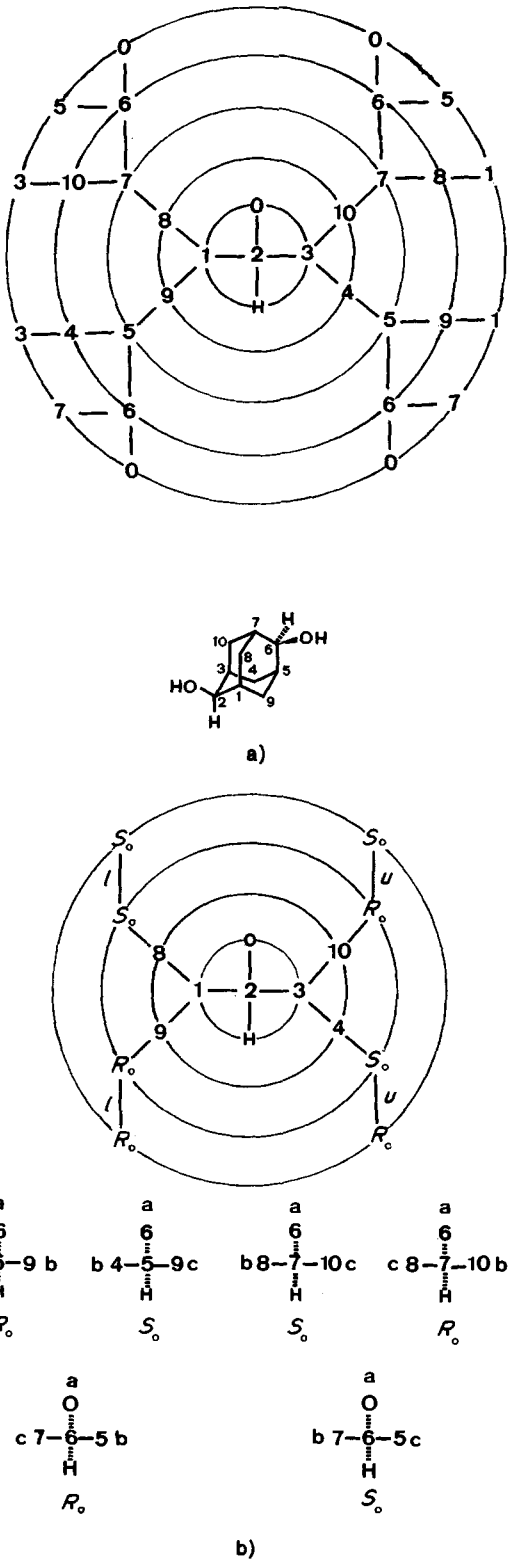


Fig. 27. Hierarchical digraphs and auxiliary descriptors of C-2 in (*S*)-2,6-adamantanediol.

at C-2 and (C-5, C-7) at C-6. Figure 27a shows the hierarchical digraph of stereogenic carbon atom 2. Ligands at C-1 and C-3 exhibit no constitutional differences and they must be different geometrically. On the basis of constitutional differences one first assigns auxiliary descriptors to stereogenic atoms C-5, C-7, and C-6. It then follows from Figure 27b that the ligand at C-1 contains two like (*l*) auxiliary descriptor pairs, and that at C-3 two unlike (*u*) ones, from which it follows that C-1 > C-3 and the descriptor is 2*S*. In accordance with the molecule's C_2-symmetry one then arrives at the descriptor 6*S*.

6.2.3. *R. S. Cahn's Cyclobutane Derivatives*

Among molecules with mutually interdependent stereogenic atoms of different type the four test cases suggested by *Cahn* (cf. [7,33]) (Fig. 28) deserve special mention. After

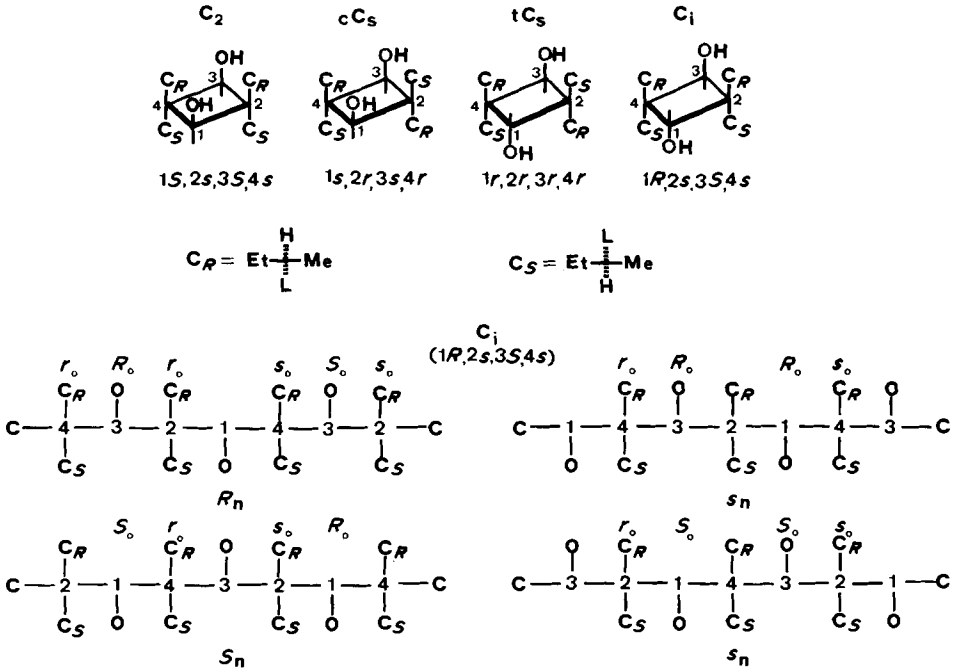


Fig. 28. Descriptors of the four diastereomeric cyclobutane derivatives. Hierarchical digraphs of stereogenic atoms in C_i diastereoisomer.

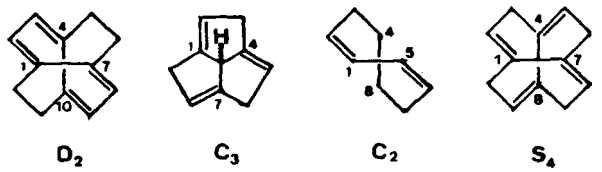
and then evaluating the others through their topological distance from this atom on the hierarchical digraph. The examples in Figure 29a—c show how the ligands can be thus ranked clearly and simply. The chiral molecule with point symmetry D_2 has a stereogenic central atom with four rotationally equivalent proximal atoms; the chiral molecule with point symmetry C-3 has three such proximal atoms. In the chiral molecule with point symmetry C_2 we find a stereogenic central atom with two rotationally equivalent proximal atom pairs.

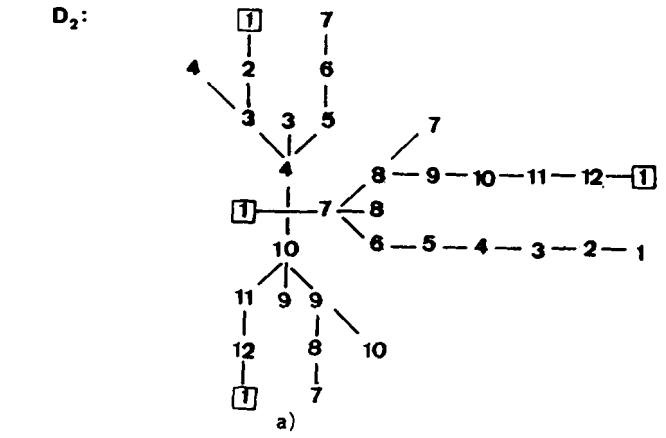
The fourth example in Figure 29d is of interest since it deals with an achiral molecule with S_4-point symmetry. The central atom is not stereogenic. Going through the above exercise using atoms C-1 and C-7 as reference atoms one arrives at a sequence leading to descriptor *R*, and using atoms C-4 and C-11 as reference one obtains descriptor *S*. These descriptors cancel each other out. This result constructing the requisite hierarchical digraphs it emerges that in all four examples the stereogenic atoms are all specifiable using symmetry-concordant descriptors; this is exemplified *in extenso* by digraphs with the stereoisomer having C_i point symmetry.

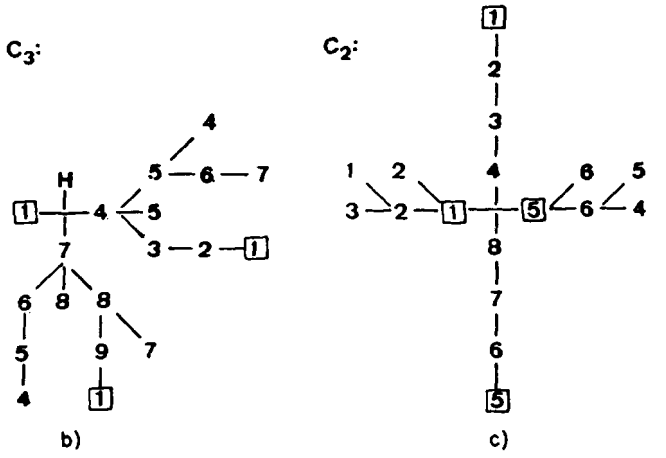
6.3. Ligands of Rotationally Symmetric Stereogenic Atoms which are Topologically Distinguishable

Proximal atoms in a polydentate ligand of a tetrahedral stereogenic atom need not necessarily be different; they may be rotationally equivalent and yet be distinguishable by their location relative to each other within the polydentate ligand. As demonstrated in 1966 such stereogenic atoms can be specified by arbitrarily allocating highest rank to one of the rotationally equivalent proximal atoms has been arrived at merely by consideration of the relative topological ranking of proximal atoms discernable from the hierarchical digraph, without any foreknowledge of the symmetry of the molecule. This should serve to illustrate the requirement that for determining order of sequence based on relative topological differences *all* proximal atoms must be used as reference atoms. The ligand sequences thus obtained lead to pairs of the same descriptor only in the case of chiral molecules, whereas with achiral molecules one obtains pairs of enantiomorphic descriptors.

This criterion of topological differentiation of ligand atoms attached to a central stereogenic atom in relation to one chosen freely and arbitrarily from the rank-highest equivalent (homotopic) among them can be used to specify stereogenic atoms in many different types of rotation-symmetric molecules, such as that shown in Figure 30[34] and







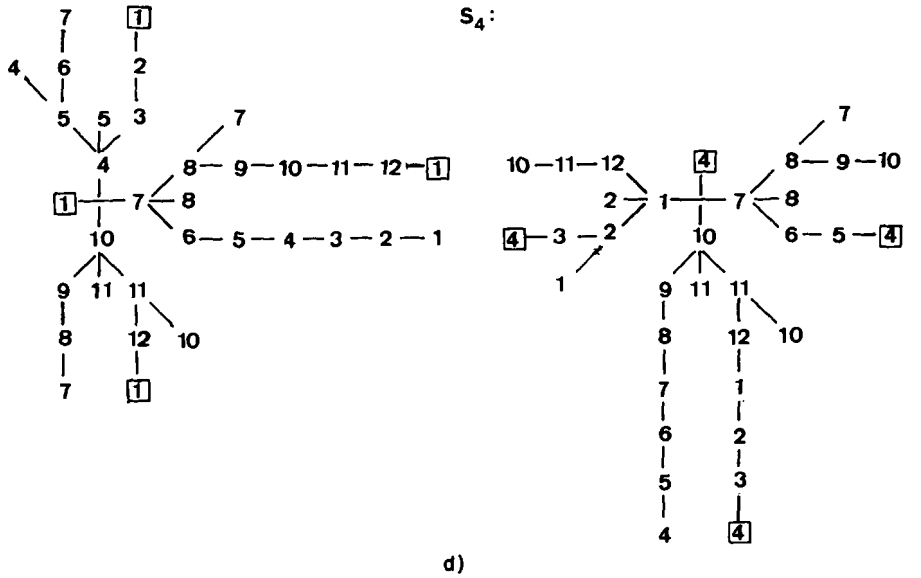


Fig. 29. Hierarchical digraphs of four molecules with rotation-symmetric topologically distinguishable ligands.

its many stereoisomers and analogues. For specifying C-1 one can use either sequence $a_1 > a_2 > b_1 > b_2$ or $a_2 > a_1 > b_2 > b_1$. Both sequences will lead to descriptor R for this and consequently for the other four stereogenic rotationally equivalent atoms.

6.4. Geometrical Enantiomorphism

Lyle and *Lyle*[35] have used the term "geometrically enantiomorphic stereoisomers" for enantiomers with constitution (A,B)X=Y(F,$\bar{F}$), where A and B are two different chiral ligands, and F and $\bar{F}$ represent an enantiomorphic ligand-pair.

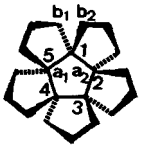


Fig. 30. A molecule with C_5 axis.

Hirschmann and *Hanson*[7] have suggested using the reflection-variant descriptors *seqCis* and *seqTrans* (note capitals!) for such enantiomers. Our example in Figure 31 shows that the enantiomer on the right can be specified using the "like" descriptor pairs *reRe* or *siSi*, and that on the left by the "unlike" pairs *siRe* or *reSi*. Since these are reflection-variant descriptor pairs, the logical abbreviations for these are *Lk* and *Ul*, respectively.

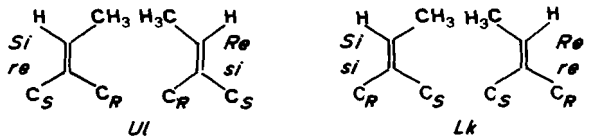


Fig. 31. Specification of "geometrically enantiomorphic" stereoisomers. C_R and C_S as in Fig. 28.

7. Epilogue

An ancient Chinese proverb states that a picture can often obviate a thousand words. One can, however, obviate thousands of pictures by means of a right word (descriptor) at the right place and a left word at the left place.

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[1] R. S. Cahn, C. K. Ingold, V. Prelog, *Angew. Chem. 78* (1966) 413; *Angew. Chem. Int. Ed. Engl. 5* (1966) 385 and previous communications [2, 3].
[2] R. S. Cahn, C. K. Ingold, V. Prelog, *Experientia 12* (1956) 81.
[3] R. S. Cahn, C. K. Ingold, *J. Chem. Soc. 1951*, 612.
[4] a) E. F. Meyer, *J. Chem. Educ. 55* (1978) 780; *J. Comput. Chem. 1* (1980) 229; b) another computer program for assignment of CIP-descriptors to stereomodels has been developed by R. Custer, Institut für Organische Chemie der Universität Zürich (personal communication).
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[7] H. Hirschmann, K. R. Hanson, *Tetrahedron 30* (1974) 3649.
[8] W. Schubert, I. Ugi, *Chimia 33* (1979) 183.
[9] Concerning the exact definition of the terms geometry and topography *Klein* [10] wrote the following comments, which have already been quoted in [6] and which, in view of their importance for understanding the subject, we requote (translated from the original German): "Geometry deals only with those relationships between coordinates which remain unaltered during substitution operations such as mentioned under 1 (*i.e.* parallel displacements, rotation about the coordinate origin, reflection and similarity transformations). In other words, geometry is the invariant theory of these operations. On the other hand, all non-invariant relationships between coordinates, *e.g.* the statement that a certain point has coordinates 2,5,3, refer to a system of coordinates which has been fixed once and for all—they belong to a science which individualizes each point and deals with the properties of each separately, namely the science of topography ...". It follows from this that chirality (orientability in Euclidean space) of a figure is a geometrical property, whereas chirality sense (the orientation of that figure and its algebraic sign) is a topographical one.
[10] F. Klein: *Elementarmathematik von höherem Standpunkt aus*, 2. ed., Springer-Verlag, Berlin 1925 (reprint 1968), p. 141.
[11] Although in principle, static stereochemistry could dispense with the use of the rather ill-defined term chemical bond, we would not consider such a move as appropriate and agree with the pointed remarks made by a mathematician, H. Weyl [12] who writes (translated from original German): "one should not take arbitrary relational representations such as valence diagrams too seriously even though they have their use in serving as a rough guide through a seemingly chaotic accumulation of facts. One cannot expect a rough sketch purporting to represent reality to contain all possible shades of that reality. Nonetheless the sketcher should have the courage of his convictions and draw the lines firmly".
[12] H. Weyl: *Philosophie der Mathematik und Naturwissenschaft*, 4th ed., Oldenbourg, München, 1976, p. 352.
[13] In order to stress the difference between molecules and models we restrict the expressions "enantiomer" and "diastereomer" to molecules and compounds only (cf. [6]). When referring to geometric and topographic interrelationships between models, ligands, or other objects we use the terms "enantiomorphic" and "diastereomorphic" (cf. [14]).
[14] K. R. Hanson, *Ann. Rev. Biochem. 45* (1976) 307.
[15] The CIP-system does not take into account diastereomers whose models are differentiated only by the magnitude of their internal coordinates (but not by their algebraic sign). Stable diastereomers of this type are exemplified by "cogwheel" stereoisomers [16]. These can be specified by using the descriptors *sp*, *sc*, *ac*, and *ap*, proposed by *Klyne* and *Prelog* [17], which indicate the approximate magnitude of torsion angles.
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[19] The algebraic sign of this volume can be defined as that of the pseudoscalar product of the three bond vectors $V = \vec{z} \cdot (\vec{y} \times \vec{x})$ in a right coordinate system.
[20] H. Gerlach, Habilitationsschrift, ETH Zürich 1971.
[21] V. Prelog, *Pure Appl. Chem. 25* (1971) 465.
[22] V. Prelog, *Science 193* (1976) 17.
[23] K. Mislow, M. Raban, *Top. in Stereochem. 1* (1967) 1.
[24] In a pamphlet issued by Chemical Abstracts Service (*A New General System for the Naming of Stereoisomers*, Columbus, Ohio, 1953, p. 2) G. E. McCasland suggested the following definitions of a stereogenic atom: "a) An atom (usually carbon) of such nature and bearing groups of such nature that it can have two different configurations. b) An atom bearing several groups of such nature that an interchange of any two groups will produce an isomer (stereoisomer)."
[25] This kind of stereoisomerism is usually denoted by the too general and hence misleading term "geometrical isomerism". In fact every diastereoisomerism is a geometrical isomerism.
[26] *J. H. van't Hoff*, the originator of the model of the "asymmetric atom", at first placed the atoms and atom groups proximal to the central atom on the faces of a tetrahedron (cf. [27]). This is feasible because replacing the vertices of a tetrahedron by its faces and *vice versa* produces an "inverse" tetrahedron. At a later stage *van't Hoff* relinquished this original idea; much later still it was taken up again as the basis of modern space-filling models.
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[28] G. L. Lemière, F. C. Alderweireldt, *J. Org. Chem. 45* (1980) 4175.
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[32] A. Werner: *Lehrbuch der Stereochemie*, Gustav Fischer, Jena 1904, p. 29.
[33] H. Hirschmann, K. R. Hanson, *J. Org. Chem. 36* (1971) 3293.
[34] We are indebted for this example to Dr. *O. Weissbach*, Beilstein-Institut, Frankfurt am Main.
[35] a) R. E. Lyle, G. G. Lyle, *J. Org. Chem. 22* (1957) 856; b) G. G. Lyle, E. T. Pelosi, *J. Am. Chem. Soc. 88* (1966) 5276.

Induction of Asymmetry by Amino Acids

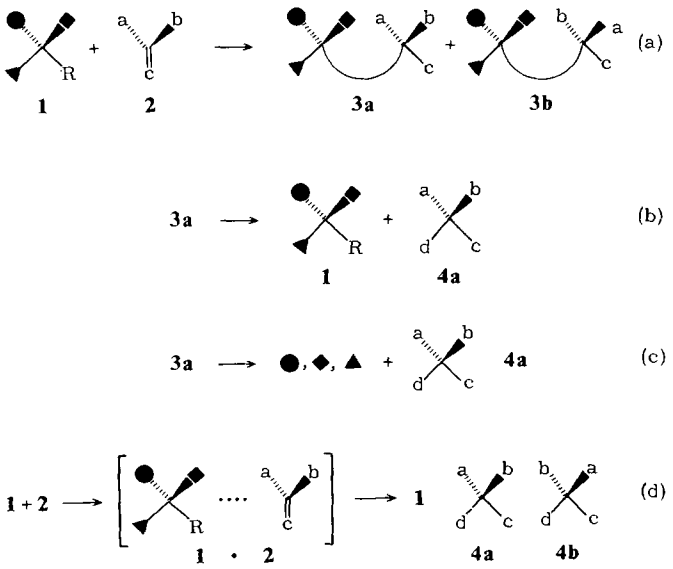
By Karlheinz Drauz, Axel Kleeman, and Jürgen Martens*

Dedicated to Professor Friedrich Asinger on the occasion of his 75th birthday

Since the stereoisomers of molecules with one or more asymmetric centers often exhibit different biological activities (*e.g.* thalidomide, pheromones), stereoselective synthesis as a method of preparative chemistry is rapidly attaining importance. Of the numerous drugs prepared by total synthesis that contain at least one asymmetric center, only about 20% have so far been used in sterically pure form. Amino acids constitute the greatest "chiral pool" of compounds whose enantiomers can be obtained commercially in large amounts; they are gradually being used more and more frequently as auxiliary agents or educts in asymmetric syntheses.

1. Introduction

The individual reaction steps of a multistep synthesis should proceed as selectively as possible, since normally the desired result is either *one* or *predominantly one* product. Depending on the nature of the synthesis, a distinction is drawn between regioselective (formation of compounds with defined constitution), diastereoselective (formation of compounds with defined relative configuration), and enantioselective reactions (formation of compounds with definite absolute configuration). The last two terms can be included under the common term of stereoselective reactions. If a compound has one chiral center, a reaction at a prochiral center with the formation of a second center of chirality leads, in principle, to two diastereomers.



When prochiral molecule **2** reacts with chiral molecule **1** to form a new center of chirality, two diastereomers, **3a** and **3b** [eq. (a)], are formed. The *de* value (%) (de = diastereomeric excess) is used as a measure of the diastereoselectivity of the reaction:

$$de = \frac{[\mathbf{3a}]-[\mathbf{3b}]}{[\mathbf{3a}]+[\mathbf{3b}]} \times 100\%$$

If only one of the two diastereomers **3a** or **3b** is formed, the reaction is said to be diastereospecific ($de = 100\%$). In the subsequent course of the synthesis **3a** or **3b** may be cleaved with the formation of a new enantiomer **4a** or **4b**, whereby chiral **1** is either recovered [eq. (b)] or not [eq. (c)].

If equivalent or catalytic amounts of a chiral molecule **1** react with a prochiral molecule **2**—the complex **1**·**2** is formed as intermediate—to give the new chiral compounds **4a** or/and **4b**, one speaks of an enantioselective reaction [eq. (d)]. The enantioselectivity of such a reaction is given by the enantiomeric excess (*ee*) or by the optical yield:

$$ee = \frac{[\mathbf{4a}]-[\mathbf{4b}]}{[\mathbf{4a}]+[\mathbf{4b}]} \times 100\%$$

$$\text{optical yield} = \frac{\alpha}{\alpha_0} \times 100\%$$

α = measured rotation of the product
α_0 = rotation of the pure enantiomer

General considerations and earlier results of stereoselective syntheses have been summarized in some recent reviews[1]. Other review articles describe special aspects: educts[2], types of reactions[3], spontaneous crystallization of one enantiomer[4], and absolute asymmetric syntheses[5]. The enantiomerically pure educts of asymmetric syntheses, the chiral[6] units **1**, can either be prepared in the laboratory or be isolated from natural products. As a rule, nature transforms prochiral[6] educts enantioselectively[6] into chiral products. Thus, the chemist has at his disposal a large number of chiral units among the natural products. In particular, carbohydrates[2c,3a,7], α-hydroxycarboxylic acids[8], and amino acids have found application as building blocks for asymmetric syntheses. The disadvantage of carbohydrates, which can rarely be obtained in several enantio-

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meric forms, does not exist in the case of α-hydroxycarboxylic acids such as lactic[9], mandelic[9], malic[9], and tartaric acids[9].

This is the first review on the induction of asymmetry for the case in which the compound **1** is represented by *amino acids* or their derivatives. Only those works are considered in which the formation of a *new* center of asymmetry is induced. This can take place with the simultaneous incorporation of the enantiomerically pure amino acid (or a derivative thereof) in the target molecule or by the action of catalytic amounts of this amino acid on a prochiral molecule. Reactions in which only the asymmetric center of the amino acid is modified, without the stereoselective appearance of a new chiral center, have not been considered. Enzymatically catalyzed transformations[10] of molecules are not treated here.

The (*S*)-amino acids used most frequently[11] are obtained by fermentation, extraction of protein hydrolyzates, or enzymatic cleavage of racemates. There are also specific preparation processes for the nonnatural (*R*)-amino acids[12]. All important amino acids can be obtained commercially in at least 1000-kg quantities in the two enantiomeric forms.

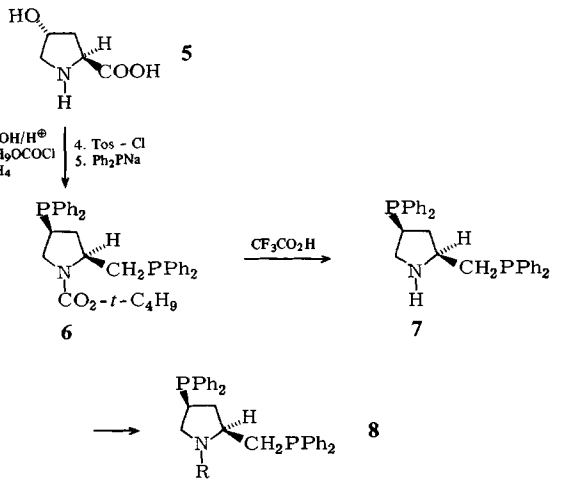
2. Induction of Asymmetry by Catalytic Amounts of Amino Acids or their Derivatives

If the chiral educts are used only as catalysts the reactions closely resemble an enzymatic process, *i.e.* an optimal process in which a small amount of chiral information is sufficient to direct a large number of molecules through the desired transformations in accordance with eq. (d).

2.1. Homogeneous Asymmetric Hydrogenation

2.1.1. Preparation of the Catalysts

A preparatively useful transfer of hydrogen to π-systems by soluble rhodium(I)-phosphane complexes such as



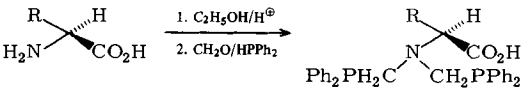
R = $OCOC_{27}H_{45}$, $COCH_3$, CO-t-C_4H_9, COC_6H_5, CO–NHC_6H_5, CONH(4-Br–C_6H_4), CONH(4-Cl–C_6H_4), CO–NH(3, 4-Cl_2–C_6H_3), CONH(4-NO_2–C_6H_4), CO–$NHCH_3$, $CONHCH{=}CHCH_3$, CONH–*cyclo*-C_6H_{11}, CHO

$(C_6H_5)_3PRhCl$ was only possible following the fundamental investigations of *Wilkinson et al.*[13].

At the beginning of this brilliant development, in 1961, came the first synthesis of optically active tertiary phosphanes by *Horner et al.*[14], which led, in 1968, to the production of chiral Wilkinson complexes with a high inductive activity by *Knowles et al.*[15]. The vigorous development in this area is reported on in a number of excellent review articles[3b,c, 16].

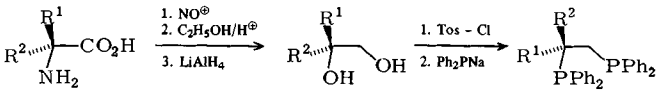
In 1976, *Achiwa*[17] synthesized the first functionalized chiral bisphosphanes based on an amino acid. Starting from 4-(*S*)-hydroxy-(*S*)-proline **5**, *Achiwa* obtained (2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (BPPM) **6** and (2*S*,4*S*)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (PPM) **7**. The bisphosphanes **8** were prepared by reaction of **7** with acid chlorides or isocyanates[18–22].

The α-amino acids (*S*)-alanine **9a** and (*S*)-valine **9b**, as well as their esters and sodium salts, can be converted into the *N*,*N*-bis(phosphinomethyl) derivatives **10** and **11**, respectively, in a modified Mannich reaction[23].



9a, R = CH_3 **10**, R = CH_3
9b, $CH(CH_3)_2$ **11**, R = $CH(CH_3)_2$

The chiral ligands (*R*)-Val-Phos (*R*)-**12** and (*R*)-Phe-Phos (*R*)-**13** have been synthesized from (*S*)-valine and (*S*)-phenylalanine, respectively[24].



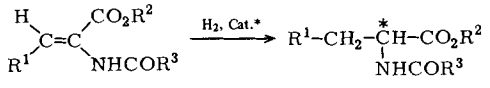
(*R*)–**12**, $R^1 = CH(CH_3)_2$, $R^2 = H$
(*R*)–**13**, $R^1 = CH_2Ph$, $R^2 = H$
(*S*)–**12**, $R^1 = H$, $R^2 = CH(CH_3)_2$
(*S*)–**13**, $R^1 = H$, $R^2 = CH_2Ph$

The chiral ligand (*R*)-1,2-bis(diphenylphosphino)propane, (*R*)-Prophos[25], has been similarly synthesized from the (*S*)-alanine derivative (*S*)-lactic acid. Starting from (*S*)-mandelic acid, *King et al.*[26], as well as *Brown* and *Murrer*[27], obtained 1,2-bis(diphenylphosphino)-1-phenylethane. *Takeuchi* and *Ohgo* have reported a less stereoselective catalyst system based on (*S*)-*N*-methylproline[28].

2.1.2. Homogeneous Asymmetric Hydrogenation of CC Double Bonds

The most spectacular results in the hydrogenation of prochiral olefins have been observed in the presence of one or two polar functional groups such as —COOH or —NHCOR. *The homogeneous-catalytic hydrogenation of dehydroamino acids* **14** leads—frequently quantitatively—to the amino acid derivatives **15** with very good optical yields (Table 1).

Achiwa et al.[21] have reported a catalytic asymmetric hydrogenation of methyl β-acetylaminoacrylate **16** with Wil-



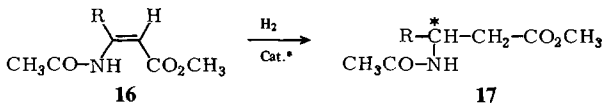
14 15

Table 1. Homogeneous catalytic asymmetric hydrogenation of dehydroamino acids **14**; $R^2 = H$.

R^1	R^3	Phosphine	**15** *ee* [%] (configuration)	Ref.
C_6H_5	CH_3	**6**	91 (*R*)	[17]
p-H_3CO—C_6H_4	CH_3	**6**	87 (*R*)	[17]
H	$OCH_2C_6H_5$	**6**	50 (*R*)	[19]
H	$OCH_2C_6H_5$	**8**, R = $COCH_3$	57 (*R*)	[19]
H	$OCH_2C_6H_5$	**8**, R = CO-*t*-C_4H_9	59 (*R*)	[19]
C_6H_5	CH_3	**8**, R = $CONHC_6H_5$	95 (*S*)	[22]
C_6H_5	CH_3	**8**, R = CONH(4-BrC_6H_4)	97 (*S*)	[22]
C_6H_5	CH_3	**8**, R = CONH(4-ClC_6H_4)	96 (*S*)	[22]
C_6H_5	CH_3	**8**, R = CONH(3,4-$Cl_2C_6H_3$)	98 (*S*)	[22]
C_6H_5	CH_3	**8**, R = CONH(4-$NO_2C_6H_4$)	95 (*S*)	[22]
C_6H_5	CH_3	**8**, R = $CONHCH_3$	94 (*S*)	[22]
C_6H_5	CH_3	**8**, R = $CONHCH{=}CHCH_3$	93 (*S*)	[22]
C_6H_5	CH_3	**8**, R = CONH-*cyclo*-C_6H_{11}	91 (*S*)	[22]
C_6H_5	C_6H_5	**6**	92 (*R*)	[29]
C_6H_5 [a]	CH_3	**10**	29 (*S*)	[23]
C_6H_5 [a]	CH_3	**11**	16 (*S*)	[23]
H	CH_3	(*R*)-**13**	85 (*S*)	[24]
H	CH_3	(*R*)-**12**	89 (*S*)	[24]
C_6H_5	CH_3	(*R*)-**13**	99 (*S*)	[24]
C_6H_5	C_6H_5	(*R*)-**12**	92 (*S*)	[24]
p-H_3CO—C_6H_4	CH_3	(*R*)-**13**	95 (*S*)	[24]

[a] $R^2 = CH_3$.

kinson complexes containing 4-(*S*)-hydroxy-(*S*)-proline derivatives as chiral ligands. The β-alanines **17** were obtained with optical yields of up to 55%.



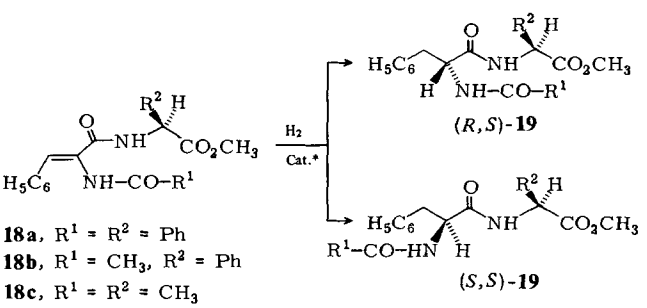
16 17

R = CH_3 or C_6H_5

Cat.* = Rhodium complex of BPPM **6**

The *stereoselective synthesis of dipeptides*[30] by hydrogenation of dehydrodipeptides[29] with rhodium complexes as catalysts has recently been reported. Regarding the induction of asymmetry, the BPPM complexes were superior to the corresponding DIOP complexes (DIOP = *P,P'*-[2,2-dimethyl-1,3-dioxolane-4,5-bis(methylene)]bis(diphenylphosphane)) and to other bis(diphenylphosphane)rhodium complexes (a diastereomeric excess of 90—95% was generally obtained[30a]).

Kagan et al.[30c] have demonstrated that the species (*S*)-**18** are hydrogenated to the diastereomers (*S,S*)-**19** with an



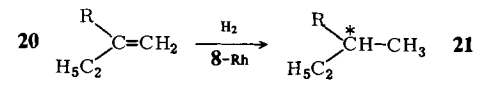
18a, $R^1 = R^2 = Ph$
18b, $R^1 = CH_3$, $R^2 = Ph$
18c, $R^1 = R^2 = CH_3$
18d, $R^1 = CH_3$, $R^2 = CH_2Ph$

(*R,S*)-**19**

(*S,S*)-**19**

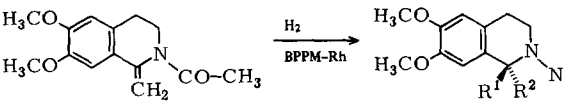
especially high optical yield when chiral Wilkinson complexes which show a pronounced (*S*)-stereoselectivity in the hydrogenation of (*Z*)-*N*-acetyldehydrophenylalanines are used; on the other hand, Wilkinson complexes that have an (*R*)-stereoselectivity in α-amino acid syntheses lead in the hydrogenation of **18** predominantly to (*R,S*)-**19**. However, the stereoselectivity is not very pronounced. This is explained by the fact that two asymmetry inducing centers—one in the catalyst, one in the educt—influence the course of the reaction; the effects can mutually augment or compensate each other. *Ojima* and *Suzuki*[30a] have also found that the (*S*)-chiral center in **18** has almost no influence on the stereoselectivity of chiral Wilkinson complexes in the synthesis of the dipeptide **19**. The stereoselective synthesis of dipeptides by asymmetric hydrogenation of dehydrodipeptides could attain preparative importance, since polypeptides with a "nonnatural" configuration at one center of asymmetry could also be synthesized by this method; these often have completely different biological activity from the natural peptides[65].

Stereoselective Hydrogenation of Other Prochiral Olefins: The hydrogenation of the olefinic double bond in the pure hydrocarbons **20** in the presence of **8**-Rh yielded only



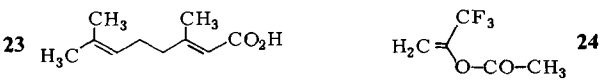
a, R = $(CH_2)_3CH_3$, **b**, R = C_6H_5

small enantiomeric excesses[18]; the same applies for the asymmetric hydrogenation of the olefinic double bonds in **22**[32a], **23**[32b], and **24**[32c] using Wilkinson complexes containing BPPM as the chiral ligand.



22

(*R*)-**25**, R^1 = H, R^2 = CH_3
(*S*)-**25**, R^1 = CH_3, R^2 = H

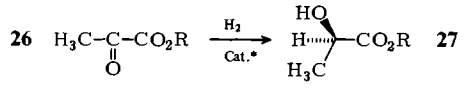


23 **24**

22, an intermediate in the synthesis of the natural compound salsolidine **25**, has also been hydrogenated[32a] in the presence of the rhodium complex of **8**; here too the optical yields were only moderate.

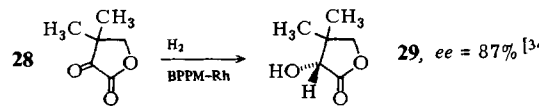
2.1.3. Homogeneous Asymmetric Hydrogenation of CO Double Bonds

Many chiral alcohols are important intermediates for the synthesis of complex molecules; unfortunately, however, there are few reports of the asymmetric reduction of carbonyl groups. Especially high optical inductions have been achieved with catalysts which contain BPPM (**6**), PPM (**7**), or **8** as chiral ligands. The pyruvic acid esters **26** were usually hydrogenated to the lactic acid esters **27** in quantitative chemical yields with an enantiomeric excess of 65 to 75%[18,33].



R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, i-C_4H_9

(*R*)-(−)-Pantolactone **29**, an important intermediate for the preparation of pantothenic acid, has been obtained with high stereoselectivity by the asymmetric hydrogenation of ketopantoyllactone **28** in the presence of a rhodium complex of BPPM[34a,b]. If **28** is hydrogenated in the presence of Rh-**8** (R = CO-*t*-C_4H_9), a smaller enantiomeric ex-



cess is obtained[34b]; with Rh-**7** the optical induction is even weaker[34b] and, moreover, the other enantiomer is obtained.

2.2. Heterogeneous Asymmetric Hydrogenation

A great advantage of heterogeneous catalysis, the ease of separating the catalyst from the product, is gained at the expense of the great disadvantage of its lower selectivity. All attempts to modify solid surfaces with optically active substances have so far given catalysts of only low stereoselectivity. This is due to the fact that too many active centers of different structures are present on the surfaces of solids. Consequently, in asymmetric hydrogenations homogeneous catalysis is superior to heterogeneous catalysis[35].

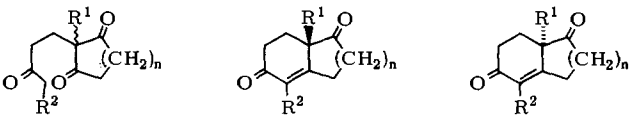
Enantioselective Raney nickel catalysts modified with chiral amino acids[36] or amino acid derivatives (α-hydroxycarboxylic acids[36d,37], dipeptides[38]) gave only very moderate enantiomeric excesses of between 0 and 10% in the hydrogenation of olefins, carbonyl compounds or oximes. Only on modification of the Raney nickel with (*S*)-tyrosine was a higher enantiomeric excess obtained[36a]. *Beamer et al.*[39] investigated enantioselective hydrogenations of α-methylcinnamic acid and of α-acetylaminocinnamic acid using palladium catalysts on chiral poly(amino acid) supports; however, the enantiomeric excesses did not exceed 6%.

An excellent review of the problems of the enantioselective heterocatalytic hydrogenation of prochiral double bonds has been compiled by *Izumi*[40].

2.3. Asymmetric Aldol Addition

According to *Weichert et al.*[41] and *Hajos et al.*[42], prochiral triketones **30** can be converted into optically active enediones **31** or **32**[41-47] with the aid of optically active catalysts having a primary or secondary amino group at the asymmetric center. More than 15 amino acids have so far been used as chiral auxiliaries[3a,47]. It is remarkable that in the cases described[41-46] catalysts of the (*S*)-series, to which most natural α-amino acids belong, cause the formation of an excess of **31**, *i.e.* they induce the (*S*)-configuration. Chiral auxiliaries of the (*R*)-series, on the other hand, lead predominantly to **32**, which has the (*R*)-configuration. The natural steroids have the same absolute configuration at C(13) as **31**.

The most thoroughly investigated reaction is the asymmetric cyclization of 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione **30a**; the resulting enedione **31a** was used as the C,D-unit in the total syntheses of steroids having natural configuration[44,48-51]. With (*S*)-proline[3a], an enantiomeric excess of 95% was achieved in almost quantitative chemical yield[2a,52] (Table 2).

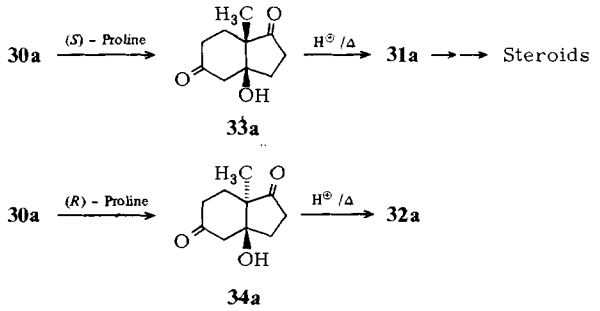


30 **31** **32**

a, R^1 = CH_3, R^2 = H, n = 1; **b**, R^1 = CH_3, R^2 = H, n = 2;
c, R^1 = C_2H_5, R^2 = H, n = 1; **d**, R^1 = CH_3, R^2 = CH_3, n = 1;
e, R^1 = CH_3, R^2 = $(CH_2)_2$-(3-CH_3O-C_6H_4), n = 1;
f, R^1 = CH_3, R^2 = $(CH_2)_2CO_2CH_3$, n = 1;
g, R^1 = CH_3, R^2 = $(CH_2)_2$-2(6-CH_3-pyridyl), n = 1.

Table 2. Asymmetric aldol cyclizations induced by chiral amino acids or amino acid derivatives.

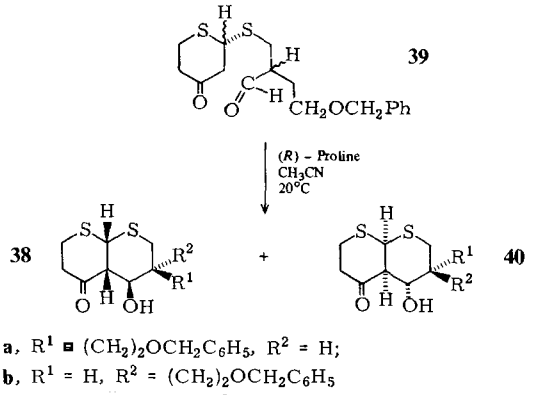
Educt **30**	Amino acid or amino acid derivatives	Solvent	Product	Yield [%] chemical	Yield [%] optical	Ref.
a	(*S*)-Proline	CH_3CN	**33a**	97	97	[42]
		DMF	**33a**	100	93	[42]
		DMF	**31a**	97	94	[47]
		CH_3CN	**31a**	90	82	[47]
a	(*S*)-Proline, $HClO_4$	CH_3CN	**31a**	87	84	[41]
a	(*R*)-Proline	DMF	**32a**	87	92	[47]
a	(*R*)-Proline, $HClO_4$	CH_3CN	**32a**	75	67	[41]
a	(*S*)-Prolinol	CH_3CN	**33a**	59	17	[42]
a	(*S*)-Homoproline [53]	DMF	**32a**	58	99	[47]
		CH_3CN	**32a**	11	90	[47]
			34a		62	[54]
a	(*R*)-Homoproline [53]	DMF	**31a**	99	58	[47]
			33a		63	[54]
a	(*S*)-2-Pyrrolidine-propionic acid [47, 55]	DMF	**31a**	47	7	[47]
		CH_3CN	**31a**	90	19	[47]
a	(*S*)-Proline pyrrolidide	CH_3CN	**31a**	79	19	[56]
		EtOH	**31a**	81	19	[56]
		THF	**31a**	86	20	[56]
		Toluene	**31a**	79	24	[56]
a	(*S*)-Proline methyl ester	Toluene	**31a**	80	17	[56]
a	(*S*)-Proline ethyl ester	CH_3CN	**31a**	18	6	[42]
a	(*S*)-Azetidine-2-carboxylic acid	CH_3CN	**33a**	51	64	[42]
a	(*S*)-Phenylalanine	DMF	**31a**	25	85	[47]
		CH_3CN	**31a**	20	91	[47]
a	(*S*)-3-Amino-4-phenylbutyric acid [47]	DMF	**32a**	80	83	[47]
		CH_3CN	**32a**	90	57	[47]
a	(*R*)-4-Amino-5-phenylvaleric acid [47]	DMF	**32a**	65	42	[47]
		CH_3CN	**32a**	62	31	[47]
c	(*S*)-Proline	DMF	**33c**	71	100	[42]
c	(*S*)-Proline, HCl	DMF	**31c**	76	80	[41]
d	(*S*)-Alanine, $HClO_4$	CH_3CN	**31c**	69		[41]
e	(*S*)-Phenylalanine, $HClO_4$	CH_3CN	**31e**	60	92	[41]
e	(*S*)-Proline pyrrolidide	Toluene	**31e**	60	31	[57]
f	(*S*)-Phenylalanine	CH_3CO_2H	**31f**	55	64	[41]
g	(*S*)-Proline, $HClO_4$	CH_3CN	**31g**	67	26	[46]
g	(*S*)-Phenylalanine, $HClO_4$	CH_3CN	**31g**	82	86	[45, 46]
g	(*S*)-Tryptophan, $HClO_4$	CH_3CN	**32g**	70	78	[46]
g	(*S*)-Serine, $HClO_4$	CH_3CN	**31g**	77	35	[46]
g	(*S*)-Valine, $HClO_4$	CH_3CN	**32g**	72	21	[46]
g	(*S*)-Tyrosine methyl ester, $HClO_4$	CH_3CN	**31g**	82	84	[46]



Hajos and *Parrish*[42] have shown that in the presence of only 3 mol-% of (*R*)- or (*S*)-proline in dimethylformamide (DMF) at room temperature **30a** is converted into the aldols **33a** and **34a**, respectively, which upon heating with *p*-toluenesulfonic acid in benzene readily eliminate water.

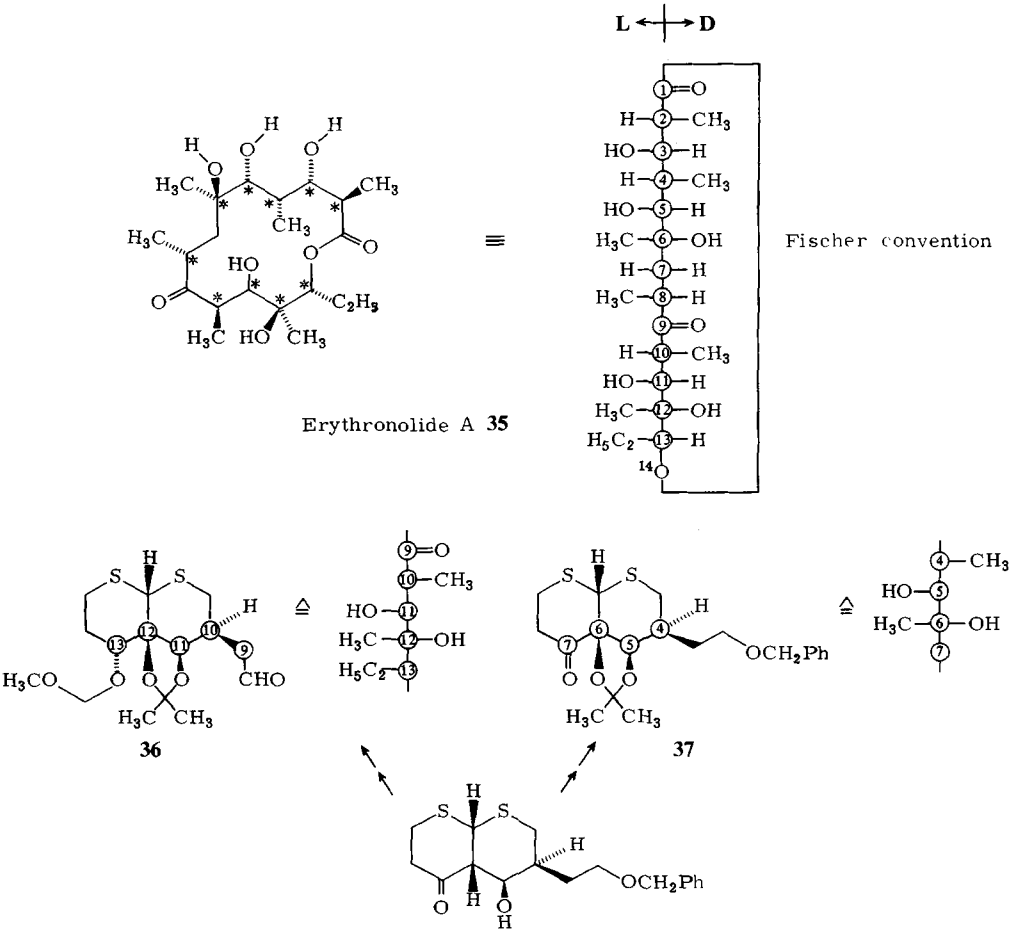
If **30a** is heated in acetonitrile in the presence of 40 mol-% of (*S*)-proline and a trace of anhydrous perchloric acid, **31a** is obtained directly[41] in 87% chemical and 84% optical yield. Table 2 summarizes the most important results of asymmetric aldol cyclizations induced by amino acids and amino acid derivatives. The best chemical and optical yields are obtained on using (*S*)- or (*R*)-proline. Numerous 19-norsteroids are prepared on a commercial scale from the products of the intramolecular aldol additions[3a]. The exact mechanism of the reaction is still unclear, but several proposals have been put forward for discussion[3a,8].

Recently, *Woodward*[58] reported advances in the synthesis of erythronolide A **35**. Careful analysis of the stereochemistry of **35** shows that the substitution patterns and configurations of the asymmetric centers at C-10, C-11, and C-12 on the one hand and at C-4, C-5, and C-6 on the other are identical. Therefore, both key substances, the aldehyde **36** and the ketone **37**, can be prepared from one and the same compound **38**.



The asymmetric synthesis of **38a** is achieved by intramolecular, (*R*)-proline-catalyzed aldol addition on the racemic dicarbonyl compound **39**[59].

38a and **40a** (7 : 3) as well as **38b** and **40b** are formed in equal chemical yields and can easily be separated from one another[59]. The CC bond formation observed in the intramolecular aldol addition leads with high selectivity to

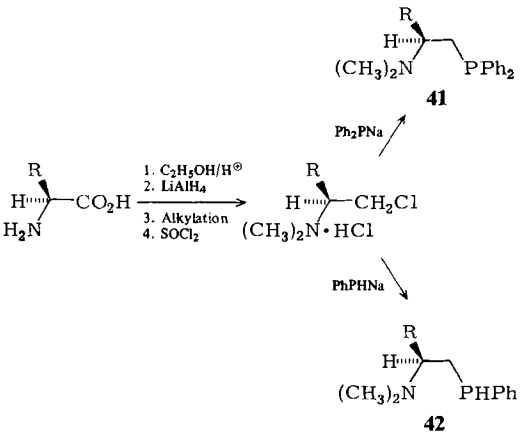


the *cis*-decalin system **38** and **40**; the (*S*)-proline-catalyzed intramolecular aldol addition of **30b**[41,60], which provides potential AB-ring synthons for steroid syntheses, proceeds analogously.

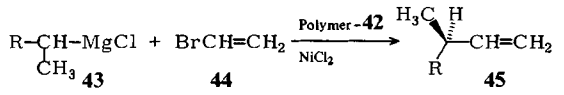
Especially striking in the asymmetric aldol additions described in this section is the particularly high stereoselectivity of the reactions catalyzed by proline and its derivatives.

2.4. Stereoselective CC Bond Formation with Grignard Reagents

Recently, *Kumada et al.*[61,62] reported on asymmetric CC coupling reactions with Grignard reagents, in which the chiral amino acid derivatives **41** or **42** — after immobilization — are used as catalysts. They can be prepared from (*S*)-valine (where R = *i*Pr) or (*S*)-phenylalanine (where R = $CH_2C_6H_5$)[61,62].



In the presence of **42**[61], which was immobilized with chloromethylated polystyrene, the nickel-catalyzed asymmetric coupling of the racemic Grignard compounds **43** with vinyl bromide **44** proceeds enantioselectively ($ee \leq 50\%$)[61].



R = C_6H_5, *p*-CH_3–C_6H_4, 2-Naphthyl

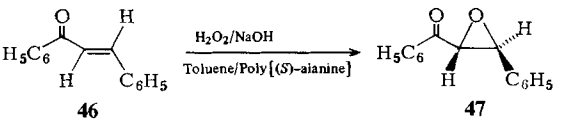
The enantiomeric excesses in similar reactions[62] with immobilized **41**[62] were smaller, and also the chemical yields were lower.

2.5. Asymmetric Cyanohydrin Syntheses

So far, optical yields of about 20% have been achieved for the addition of hydrocyanic acid to aldehydes using linear or cyclic dipeptides derived from histidine and alanine as catalysts[63a,b]. Recently, *Inoue et al.*[63c] reported *ee* values of up to 90% for the addition of HCN to benzaldehyde with *cyclo*-(*S*)-phenylalanyl-(*S*)-histidine as catalyst.

2.6. Stereoselective Epoxidation

Julia et al.[64] recently reported the first example of an almost stereospecific epoxidation catalyzed by a readily available synthetic chiral polypeptide. With poly[(*S*)-alanine] as catalyst, chalcone **46** is epoxidized, with a good chemical conversion, to the levorotatory epoxide **47** ($ee \geq 90\%$)[64]. If the poly[(*S*)-alanine] is replaced by poly[5-benzyl-(*S*)-glutamate] or poly[5-butyl-(*S*)-glutamate], both the optical and the chemical yields of **47** are markedly lower[64]. Without the addition of poly(amino acids) no epoxidation occurs under the reaction conditions, which indicates that the reaction takes place at the boundary of the chiral phase. Synthetic peptides prove to be interesting alternatives to enzymes as stereoselective catalysts[65].



3. Transfer of Asymmetry

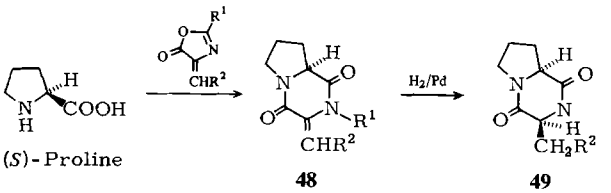
In the preceding section we considered the induction of asymmetry by *catalytic* amounts of "chiral information" (amino acids and their derivatives). The chiral information is transferred onto a prochiral substrate. In this section we turn to reactions in which at least *equimolar* amounts of chiral information are required for the induction of asymmetry. The newly formed asymmetric center can be induced by either intramolecular or by intermolecular interactions.

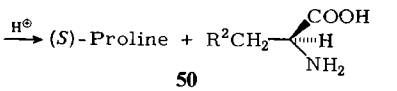
3.1. Hydrogenations

3.1.1. Asymmetric Hydrogenation of CC Double Bonds

If it is desired to hydrogenate C=C bonds asymmetrically in the presence of achiral catalysts, chiral information must be present in the substrate. In the catalytic hydrogenation of peptides and cyclopeptides containing dehydroamino acid units, the chiral center of the neighboring amino acid frequently brings about an intramolecular induction of asymmetry[30,66,67]. The optical yields have always been lower than 50% for the hydrogenation of open-chain dehydrodipeptides **18** in the presence of achiral catalysts in homogeneous or heterogeneous phase[30a,d,66c–e].

On the other hand, excellent optical yields have been obtained for the hydrogenation of bicyclic piperazinediones **48**; according to *Poisel* and *Schmidt*[66d], the best stereoselectivity is achieved in the case of (*S*)-proline de-

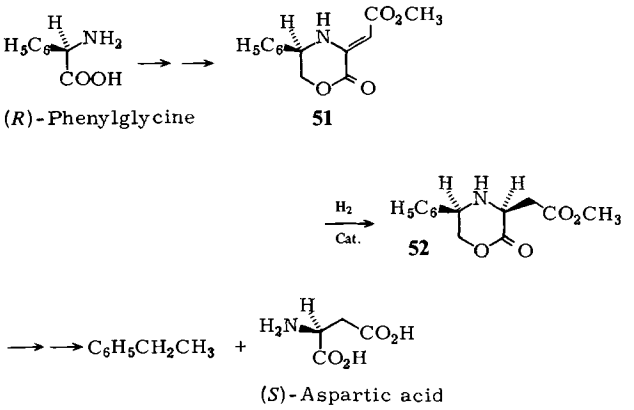




R^1 = H, CH_3; R^2 = Aryl[66d], Alkyl[66b]

rivatives. *Hydrolysis* of the resulting (*S,S*)-cyclodipeptides **49** (*ee* > 90%) affords the chiral amino acids **50** and (*S*)-proline.

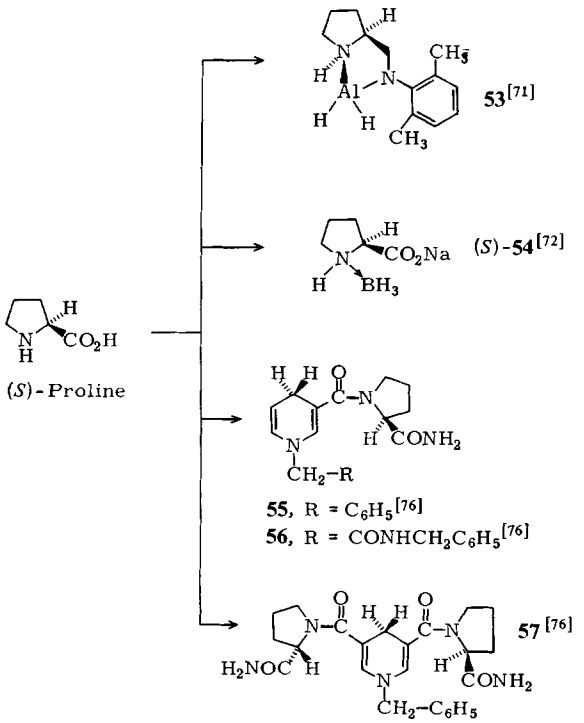
In the asymmetric hydrogenation of the olefinic double bond of (*R*)-phenylglycine derivative **51** in the presence of achiral catalysts the stereoselectivity was always low (*ee* ≤ 17%)[68]. The preferred formation of **52** can be attributed to the influence of the bulky phenyl residue in **51**. **52** could subsequently be converted into (*S*)-aspartic acid. This synthesis, carried out by *Tamura* and *Harada*[68], is an example of the transfer of chirality with subsequent disappearance of the original chiral center.



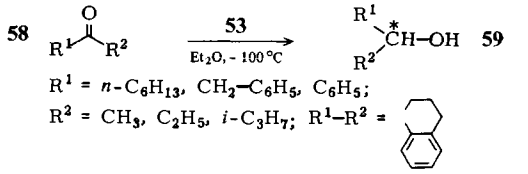
The asymmetric hydrogenation of a CC double bond in a total synthesis of gephrytoxin with diisobutylaluminum hydride has been described by *Kishi et al.*[69]. Optically active pyrrolizidine bases have been synthesized by *Robins* and *Sakdarat*[70] by hydrogenation of a chiral hydroxyproline derivative (*de* > 60%).

3.1.2. Asymmetric Hydrogenation of CO Double Bonds

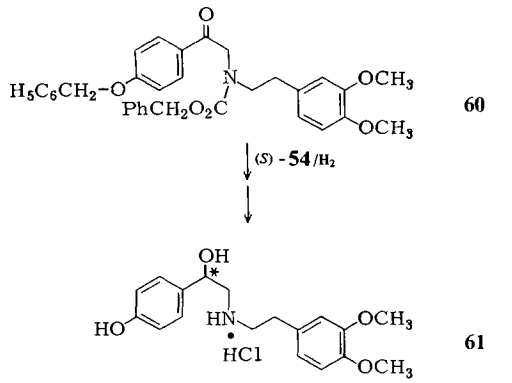
The reducing agents **53** to **57**, derived from (*S*)-proline, are eminently suitable for the hydrogenation of prochiral ketones.



The ketones **58** are reduced with **53** at −100 °C in high chemical (82—97%) and optical (31—96%) yields[71] to the (*S*)-alcohols **59**. The chiral precursor of **53** can be recovered.



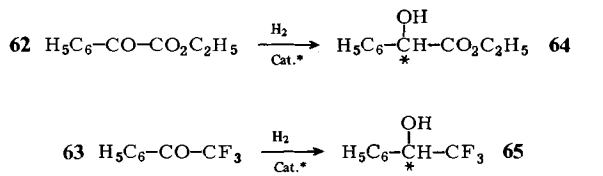
The BH_3-adduct (*S*)-**54** reduces prochiral aryl alkyl ketones and dialkyl ketones to the corresponding chiral alcohols in chemical yields of 66 to 92% and optical yields of up to 62%[72]. (*S*)-**54** has also been used as a stereoselective reducing agent for the hydrogenation of the ketone **60** with formation of the HCl-adduct **61**, which is used as a drug.



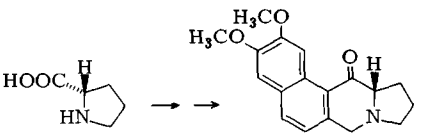
Reduction of the ketones **58** with the mirror image of (*S*)-**54**, *i.e.* (*R*)-**54** derived from the nonnatural (*R*)-proline, gave the expected alcohols with the inverted configuration[72].

The stereochemistry of NADH model reactions is of special interest to biochemists who wish to study the origin of the induction of asymmetry in such reactions. Thus, the influence of peptide derivatives[73] on the course of NADH model reactions, the incorporation of chiral 1,4-dihydronicotinamide in crown ethers[74], and electronic factors[75] which influence NADH model reactions have been investigated. *Inouye et al.*[76] obtained the chiral alcohols **64** and **65** in yields of up to 84% (*ee* ≤ 83%) from the asymmetric reduction of the corresponding prochiral carbonyl substrates **62** and **63** with (*S*)-prolinamide derivatives of 1,4-dihydronicotinamide such as **55** to **57** and ionic metal catalysts ($Mg(ClO_4)_2$, $ZnCl_2$ or $CoCl_2$).

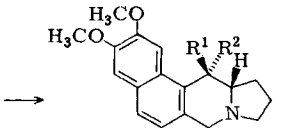
It is striking that the cyclic amino acid proline is the source of the chiral information in the particularly selective hydrogenation catalysts **53** to **57**, while the stereoselectivity of chiral catalysts derived from acyclic amino acids leads maximally to an optical yield of 23%.



Wiegrebe et al.[78] found that the (*S*)-proline derivative **66** is preferentially hydrogenated to **67a**.



(*S*)-Proline **66**

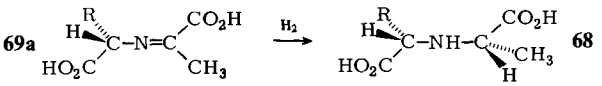


67a, R^1 = H, R^2 = OH
67b, R^1 = OH, R^2 = H

With $LiAlH_4$ or $NaBH_4$ (in 70% ethanol) the diastereomers **67a** and **67b** are formed in a ratio of 4:1 ($LiAlH_4$) or 2:1 ($NaBH_4$)[78]. The same diastereoselectivity was achieved by *Crooks* and *Rosenberg*[79] for the reduction of a keto function in a spiro compound derived from proline.

3.1.3. Asymmetric Hydrogenation of CN Double Bonds

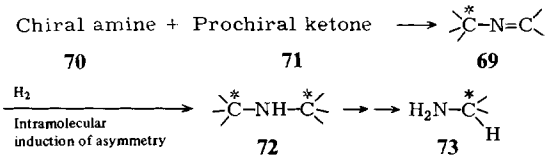
As early as 1939 *Knoop* and *Martius*[80] reported the synthesis of isooctopine **68**[81] by the hydrogenation of the Schiff base **69a** obtained from (*S*)-arginine and pyruvic acid.



69a **68**

R = $(CH_2)_3NHC(NH_2)=NH$

A whole series of such chemical transaminations from optically active amino acids[80] and amino acid derivatives



70 **71** **69** **72** **73**

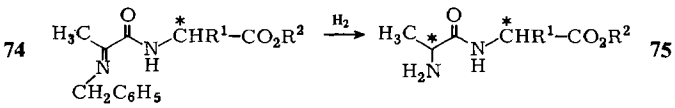
70 (esters[81], amino alcohols[82]) to carbonyl functions in **71** (α-keto acids[80], α-keto esters[81,82], ketones[81b]) are known today. In each case a Schiff base **69** is an intermediate.

It can be seen from a comparison of the asymmetric hydrogenations of CC and CN double bonds (see Tables 1 and 3) that considerably lower *ee* values were achieved in the latter.

In the reduction of the Schiff base **69** to the secondary amine **72**, an intramolecular transfer of asymmetry takes place. **72** can be converted by further reactions into a chiral primary amine **73**. The mechanism[80c] and the temperature dependence[80d] of such reactions have been investigated by *Harada et al.* Better optical yields are obtained in nonpolar solvents, such as benzene, than in polar solvents such as methanol[81c].

In the copper(II)-pyridoxal-catalyzed nonenzymatic transamination between (*S*)-alanine or (*S*)-phenylalanine and α-ketoglutaric acid formation of (*S*)-glutamic acid is preferred[83]. When (*R*)-alanine or (*R*)-phenylalanine is used, (*R*)-glutamic acid is formed preferentially[83].

The hydrogenation of the CN double bond in the Schiff bases **74** from achiral amides and chiral *N*-α-ketoacylamino acids[84] and their esters[85] takes place with intramolecular transfer of the chirality with concomitant cleavage of the benzyl group.



74 **75**

R^1 = CH_3, C_2H_5, i-C_3H_7, i-C_4H_9, $CH_2C_6H_5$, CH_2CO_2-i-C_4H_9
R^2 = H, CH_3, i-C_4H_9

The optical yield obtained in the hydrogenation **74**→**75** is between 17 and 64%[84,85]. On the other hand, *Iwakuma et al.*[71] and *Sunjic et al.*[86] obtained *ee* values of up to 98% in the reduction of cyclic imines.

3.2. CC Bond-Forming Reactions

In this section asymmetric CC bond-forming reactions are considered in which chiral amino acids and amino acid derivatives are used as auxiliary reagents:

Table 3. Asymmetric reduktion of Schiff bases **71**.

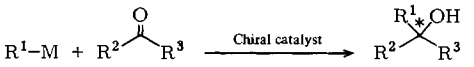
Chiral amine **69**	Prochiral ketone **70**	Product **73**	Yield (%) chemical	Yield (%) optical	Configuration	Ref.
(*R*)-Phenylglycine	CH_3COCO_2H	Alanine	35	53	*R*	[80c]
	$C_2H_5COCO_2H$	α-Aminobutyric acid	41	39	*R*	[80c]
	$HO_2C(CH_2)_2COCO_2H$	Glutamic acid	25	56	*R*	[80c]
(*S*)-Phenylglycine	CH_3COCO_2H	Alanine	35	41	*S*	[80c]
(*R*)-Phenylglycine methyl ester	$CH_3COCO_2C_2H_5$	Alanine	72	32	*S*	[81c]
(*R*)-2-Amino-2-phenyl-ethanol [a]	$CH_3COCO_2C_2H_5$	Alanine	56	62	*S* [b]	[82]
(*S*)-Phenylalanine ethyl ester	$CH_3COCO_2C_2H_5$	Alanine	73	25	*S* [c]	[82]
(*S*)-Phenylalanine *tert*-butyl ester	$CH_3COCO_2CH_3$	Alanine	58	70	*S*	[81a]
(*S*)-Leucine *tert*-butyl ester	$CH_3COCO_2CH_3$	Alanine	43	62	*S*	[81a]
(*S*)-Aspartic acid di-*tert*-butyl ester	$CH_3COCO_2CH_3$	Alanine	35	57	*S*	[81a]
(*S*)-Aspartic acid diethyl ester	$C_6H_5CH_2COCH_3$	α-Methylphenethylamine	40	49	*S*	[81b]
(*S*)-Glutamic acid di-*tert*-butyl ester	$CH_3COCO_2CH_3$	Alanine	41	53	*S*	[81a]
(*S*)-Alanine ethyl ester	$C_6H_5CH_2COCH_3$	α-Methylphenethylamine	37	66	*S*	[81b]
(*S*)-Alanine *tert*-butyl ester	$C_6H_5CH_2COCH_3$	α-Methylphenethylamine	37	85	*S*	[81b]
(*S*)-Valine ethyl ester	$C_6H_5CH_2COCH_3$	α-Methylphenethylamine	56	50	*S*	[81b]
(*S*)-Valine *tert*-butyl ester	$CH_3COCO_2CH_3$	Alanine	37	71	*S*	[81a]
	$C_6H_5CH_2COOCH_3$	α-Methylphenethylamine	63	87	*S*	[81b]

[a] Prepared from (*R*)-phenylglycine ethyl ester [82]. [b] The hydragenation was carried out in benzene. [c] The hydrogenation was carried out in methanol.

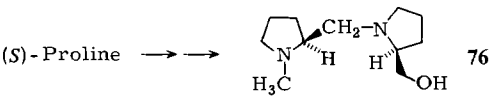
— alkylation of carbonyl compounds at the α, β, and γ position to the carbonyl group,
— Strecker syntheses,
— reactions of the Pictet-Spengler type,
— electrocyclic reactions.

3.2.1. Reactions at the Carbonyl Group

1,2-Additions of Organometallic Compounds: Many efforts have already been made to prepare optically active alcohols by the asymmetric addition of organometallic compounds to carbonyl compounds. With few exceptions, the optical yields in the addition reactions of Grignard reagents[87], alkyllithium compounds[88], organocopper[89] and organocadmium[90] compounds in chiral solvents or in the presence of chiral auxiliary reagents (ligands) are quite low[91].



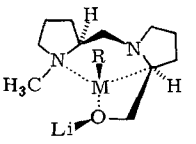
Since the prochiral substrate is only weakly bound to the chiral auxiliary reagent, the latter must be used in a considerable excess relative to the compound to be alkylated. In the addition of alkyllithium compounds to aldehydes, *Mukaiyama et al.*[92] used the (*S*)-proline derivative **76** as a new chiral ligand.



76

The reactions, which were carried out between 0 °C and −123 °C in various solvents[92], proceed in part with high optical yields (see Table 4).

Both nitrogen atoms as well as the free hydroxy group in **76** appear to be essential centers for coordination with the



77, M = Li, Mg

alkylmetal; the quasi-rigid complex **77** provides the right chiral environment for induction. Aside from alkyllithium compounds, only dialkylmagnesium compounds gave high optical yields of the alcohols[92b,93]. α-Ketoaldehydes can also be alkylated asymmetrically. For this purpose, these

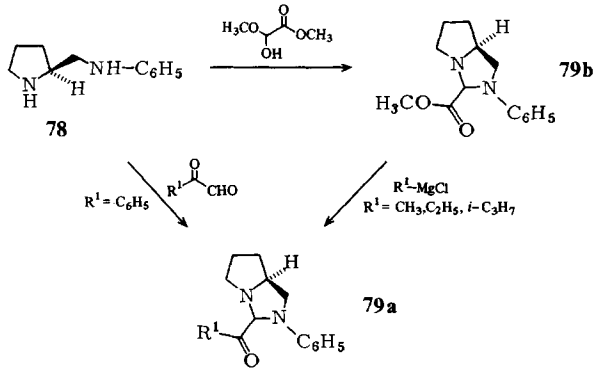


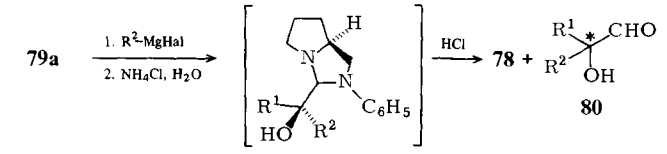
Table 4. Synthesis of optically active alkohols with the chiral ligands **76** [92]: R^1—Li + R^2—CHO → R^1R^2CHOH.

R^1	R^2	Solvent	Alcohol formed preferentially	Yield [%] chemical	optical	Ref.
CH_3	C_6H_5	$(C_2H_5)_2O$		82	21	[92b]
CH_3	C_6H_5	$CH_2(OCH_3)_2$		81	40	[92b]
C_2H_5	C_6H_5	$(C_2H_5)_2O$		32	39	[92b]
C_2H_5	C_6H_5	$CH_2(OCH_3)_2$		59	54	[92b]
C_2H_5	C_6H_5	$CH_2(OCH_3)_2$/ $(CH_3)_2O$ (1:1)		70	45	[92b]
C_3H_7	C_6H_5	$CH_2(OCH_3)_2$/ $(CH_3)_2O$ (1:1)		64	60	[92b]
n-C_4H_9	C_6H_5	$CH_2(OCH_3)_2$/ $(CH_3)_2O$ (1:1)		77	95	[92b, d]
i-C_4H_9	C_6H_5	n-C_7H_{16}		59	16	[92a]
n-C_4H_9	i-C_3H_7	$CH_2(OCH_3)_2$/ $(CH_3)_2O$ (1:1)		57	80	[92a]
R—C≡C [a]	C_6H_5	$CH_2(OCH_3)_2$		67–99 [a]	54–92 [a]	[92a]

[a] R = H, trialkylsilyl or triarylsilyl groups. The highest chemical yield was obtained with the trimethylsilyl protecting group at −78 °C and the highest optical yield with the same group at −123 °C.

are converted with the (*S*)-proline derivative **78** into the aminals **79a**. A direct synthesis of these aminals is successful only with phenylglyoxal; aminals of alkylglyoxals must be prepared from the hemiacetal of the methyl glyoxylate and **78** *via* the intermediate **79b**[94].

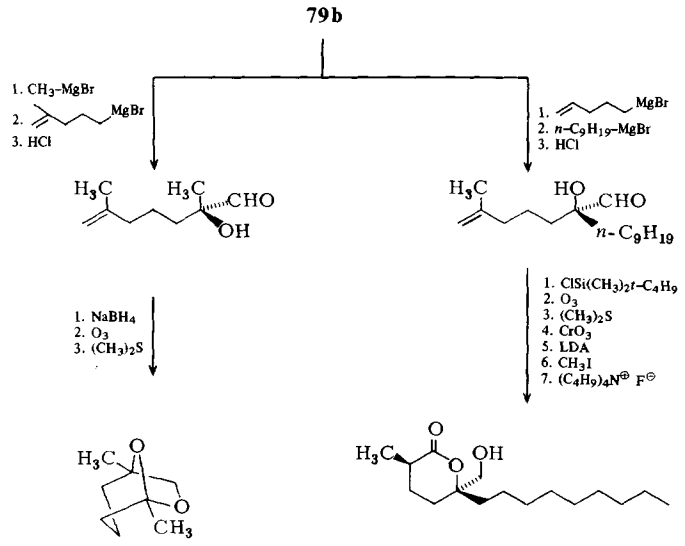
The subsequent Grignard reaction of **79a** furnishes the α-hydroxyaldehyde **80** in yields of 40 to 80% (*ee* = 75 to 100%)[94]. If, according to the CIP rules, R^1 has a higher



R^1 = CH_3, C_2H_5, i-C_3H_7, C_6H_5
R^2 = CH_3, C_2H_5, i-C_3H_7, $CH{=}CH_2$, C_6H_5

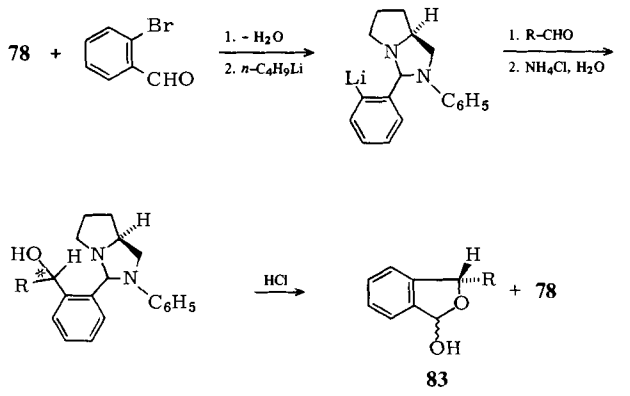
priority than R^2, then **80** has an (*S*)-configuration; otherwise it has an (*R*)-configuration.

This synthetic principle was used by *Mukaiyama et al.* in the asymmetric total synthesis of the pheromone (*R*)-frontalin **81**[95] and of the algal antibiotic (2*R*,5*S*)-malyngolid **82**[96]. In both cases the key reaction is the synthesis of an optically active α-hydroxyaldehyde. If the two Grignard reagents are added in the reverse sequence to **79b** in the synthesis of **81**, the (*S*)-frontalin is formed.

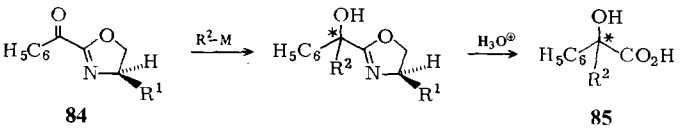


LDA = Lithium diisopropylamide

An asymmetric induction also takes place when achiral aldehydes are alkylated with chiral lithium compounds. *Mukaiyama et al.*[97] succeeded in realizing this type of reaction, again with the use of **78**. The optical yields of the lactols **83** lie between 20% (crotonaldehyde) and 90% (isobutyraldehyde). By oxidation of the lactol **83** ($R = n$-C_4H_9) with silver oxide it was possible to prepare (*S*)-3-butylphthalide, a constituent of the aroma of the celery plant, in 88% yield without racemization.

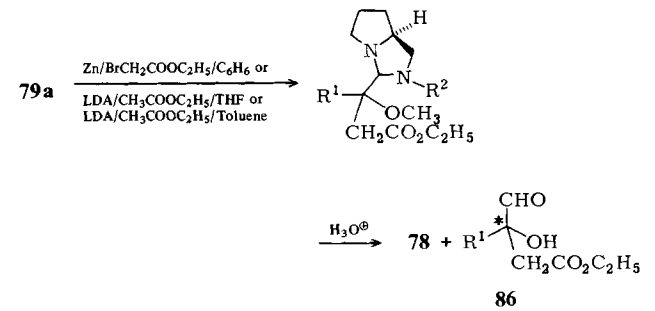


Meyers et al.[98] used the benzoyloxazolines **84**, which are derived from (*R*)-phenylglycine or (*R*)-phenylalanine, as chiral carbonyl compounds. Reaction with Grignard compounds and alkyllithium compounds yields, after hydrolysis, the optically active α-substituted mandelic acid derivatives **85** (*ee* ≤ 40%). The oxazolines **84** give substantially poorer optical induction than the proline compounds **76** and **78** used by *Mukaiyama et al.*



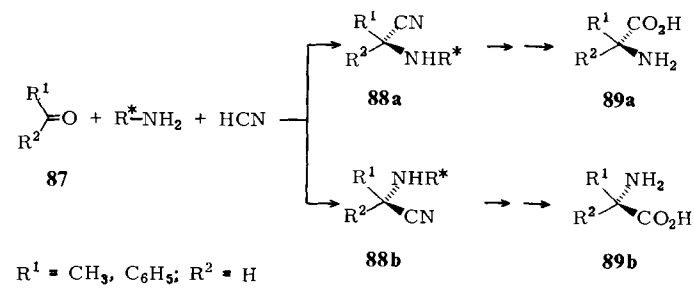
R^1 = C_6H_5, $CH_2C_6H_5$; R^2 = CH_3, C_2H_5, 4-CH_3-C_6H_4

Mukaiyama et al.[99] also carried out the alkylation of the chiral α-ketoaminals **79a** with various metal enolates of ethyl acetate. Astonishingly, even the alkylations with the zinc enolates, which were carried out in refluxing benzene, gave very high optical yields of substituted 3-formyl-3-hydroxypropionic esters **86**.



R^1 = CH_3, C_2H_5, i-C_3H_7, C_6H_5; R^2 = C_6H_5, 2-CH_3O-C_6H_5

Asymmetric Strecker Syntheses are characterized by the reaction of a carbonyl component **87** with an optically active amine and hydrocyanic acid to preferentially form one



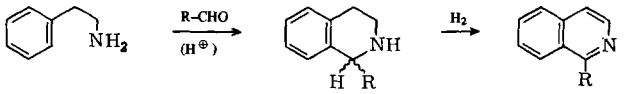
R^1 = CH_3, C_6H_5; R^2 = H

of the two diastereomeric aminonitriles **88a** or **88b**. To prepare the chiral amino acids **89a** or **89b**, **88a** or **88b** is hydrolyzed with mineral acids, whereupon R* is cleaved.

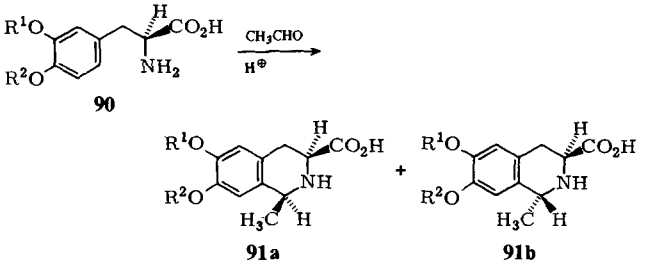
The most commonly used chiral amine in the asymmetric Strecker synthesis is α-phenylethylamine[100]. Amino acid derivatives have also been used quite successfully as chiral amines. (*S*)-*tert*-Butylglycine *tert*-butyl ester has proved to be an especially good source of chiral information, the optical yields obtained with it amounting to up to 96.5%. The best results are obtained in nonpolar solvents such as *n*-hexane[101].

The use of the asymmetric Strecker synthesis in the preparation of other chiral products has been dealt with by *Achiwa* and *Yamada*[103], and *Harada* and *Okawara*[102, 104], and reviewed by *Morrison* and *Mosher*[105]. In all of these cases an amino acid derivative is used as the chiral amine component which is responsible for the induction of asymmetry.

Reactions of the Pictet-Spengler Type: The "Pictet-Spengler reaction" has long been used in heterocyclic chemistry for the synthesis of the isoquinoline ring system; the tetrahydroisoquinoline intermediate here is a racemate.

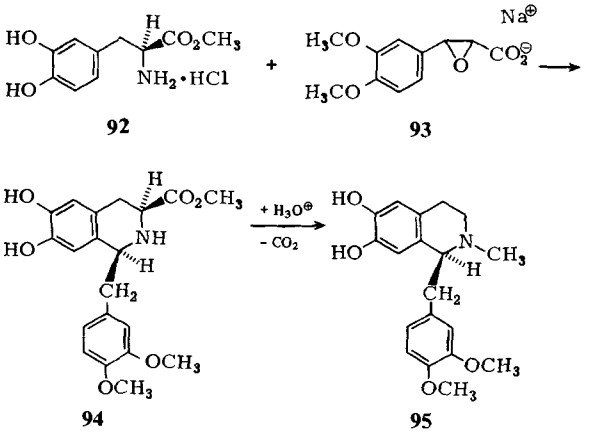


Phenylalanine and tryptophan derivatives possess a β-arylethylamine structure and can therefore take part in reactions of this type with aldehydes. The phenylalanines give rise primarily to tetrahydroisoquinolinecarboxylic acid derivatives and the tryptophans to tetrahydro-β-carbolines, which are of interest as starting compounds for alkaloid syntheses. Such carbolines were synthesized by *Snyder et al.*[106] as early as 1948, but from racemic tryptophan. In 1972, *Brossi et al.*[107] reported a Pictet-Spengler condensation of (*S*)-Dopa **90** and of its *O*-alkyl derivatives with acetaldehyde which occurred with asymmetric induction. This gave rise predominantly to the tetrahydroisoquinolinecarboxylic acids **91a** ($de \leq 80\%$) in which the carboxyl and methyl groups are in the *cis* position to one another. The absolute configuration of the products was established by X-ray structure analysis. The optically active center of the amino acid induces the configuration at C-1 with high stereoselectivity.



$R^1 = R^2 = H, CH_3$

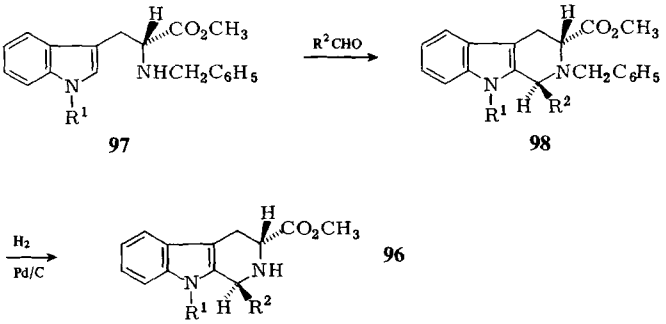
Condensation of (*S*)-dopa methyl ester hydrochloride **92** with the carboxylate **93** (precursor of 3,4-dimethoxybenzaldehyde) gives the tetrahydroisoquinoline **94** ($ee = 76\%$)[108], which, after decarboxylation (*i.e.* removal of the original asymmetric center), is converted into (*S*)-laudanosine **95**[109].



(*R*)-Laudanosine[110] and (*S*)-reticuline[111] have been prepared by the same method. Syntheses of 8- and 13-methylberberine alkaloids starting from **91a** ($R^1 = R^2 = H$) have been reported by *Rapoport et al.*[112].

The interest in β-carboline alkaloids became particularly acute after the discovery of their pharmacological activity in syndromes such as alcoholism and mental illness[113]. The pronounced sedative, analgesic, and antidepressant properties of 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines stimulated further investigations in this sector[114].

Cook et al.[115] were the first to obtain the *trans*-1,3-disubstituted β-carbolines **96** practically stereospecifically by condensing *N*-benzyltryptophan methyl ester **97** with aldehydes. The benzyl group could subsequently be removed hydrogenolytically. This exclusive formation of the *trans* isomers can be ascribed to the steric effect of the *N*-benzyl group, for a *trans* arrangement of the substituents in the 1,3-position in **98** leads to a pronounced decrease in the steric hindrance.



R^1 = H, CH_3; R^2 = C_2H_5, *cyclo*-C_6H_{11}, 2-HO-C_6H_4

3.2.2. Reactions at the α-C Atom of Carbonyl Groups

Alkylation of Imino- and Enamino Compounds: Enantioselective CC bond formation in the α-position of prochiral carbonyl compounds is one of the oldest fields of application of asymmetric syntheses. As pointed out by *Stork et al.*[116], the alkylation of an imino anion is one of the best

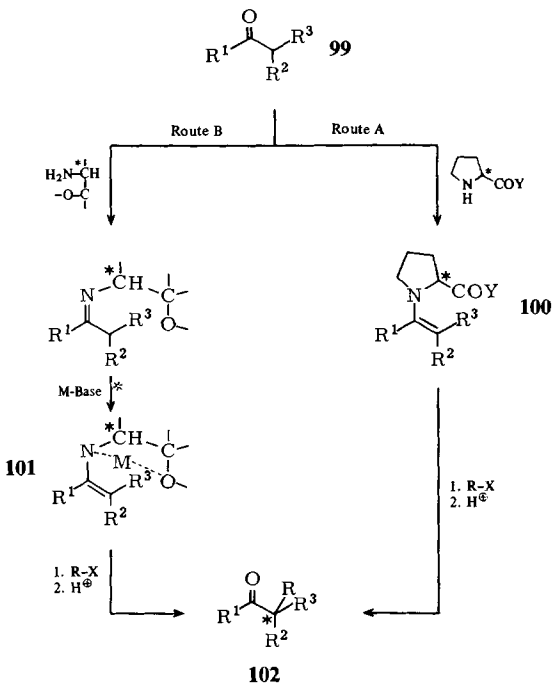
methods for the α-alkylation of ketones. If a chiral amine is used for the synthesis of the imine, the alkylation process can be carried out enantioselectively.

Horeau et al.[117] first reported as long ago as 1968 an enantioselective methylation of cyclohexanone *via* an optically active isobornylimine to 2-methylcyclohexanone (*ee* = 72%). *Kitamoto et al.*[118] used (*S*)-α-phenylethylamine and (*S*)-2-aminobutane as chiral amines but obtained optical yields of only between 6 and 30%.

The following deals only with those chiral amino compounds that are derived directly from amino acids[119].

The alkylation of cyclohexanone has been thoroughly studied as a model reaction. Generally, enamino compounds **99** of ketones are allowed to react with alkyl halides or α,β-unsaturated carbonyl compounds; the enamine **100** is prepared directly from **99** with chiral secondary amines (Scheme 1, route A). A "metalloenamine" **101** can also be synthesized from chiral imines by metalation (Scheme 1, route B). The primary amines used for the formation of imines must possess an oxygen function on a carbon atom adjacent to the asymmetric center so that the rigid chelate complex **101** is capable of forming.

A series of amines has been used (see Table 5), the best optical yields having been obtained with phenylalanine derivatives and *tert*-leucine *tert*-butyl ester **105** (see Table 5)[120].



Scheme 1.

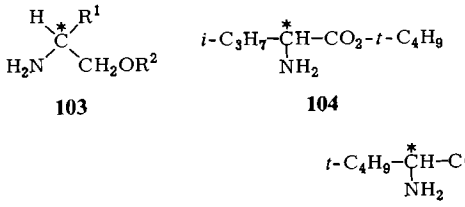


Table 6. Amino acid derivates **103–105** for the preparation of chiral chelate complexes **101** [120].

	R^1	R^2	Configuration	Educt amino acid
103a	$C_6H_5CH_2$	CH_3	(*S*)	Phe
103b	$C_6H_5CH_2$	CH_3	(*R*)	Phe
103c	$C_6H_5CH_2$	$CH_2CH_2OCH_3$	(*S*)	Phe
103d	$C_6H_5CH_2$	$CH_2CH_2OCH_2CH_2OCH_3$	(*S*)	Phe
103e	$C_6H_5CH_2$	$CH_2CH_2N(CH_3)_2$	(*S*)	Phe
103f	C_6H_5	$CH_2CH_2OCH_3$	(*R*)	Phenyl-Gly
103g	$(CH_3)_2CH$	CH_3	(*S*)	Val
103h	$(CH_3)_2CHCH_2$	$CH_2CH_2CH_2OCH_3$	(*S*)	Leu
103i	$(CH_3)_2CHCH_2$	CH_3	(*S*)	Leu
103j	$(CH_3)_2CHCH_2$	$CH_2CH_2OCH_3$	(*S*)	Leu
103k	*cyclo*-$C_6H_{11}CH_2$	CH_3	(*R*)	Hexahydro-Phe
103l	CH_3CH_2	*n*-C_4H_9	(*R*)	α-Amino-butyric acid
103m	CH_3CH_2	H	(*R*)	α-Amino-butyric acid
104			(*S*)	Val
105			(*S*)	*tert*-Leu

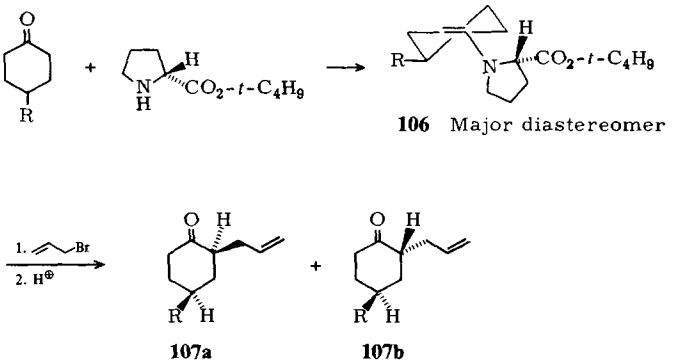
Table 5. Enantioselective alkylation of aldehydes and ketones **99** *via* chiral metal-complexes **101** (Scheme 1) [120]; $R^3 = H$, M = Li.

99 R^1	R^2	Amine	R—X	**102** Yield [%] chemical	optical (Configuration)
—$(CH_2)_4$—		**103b**	$(CH_3)_2SO_4$	72	82 (*R*)
—$(CH_2)_4$—		**103b**	*n*-C_3H_7I	50	>95 (*R*)
—$(CH_2)_4$—		**103b**	$CH_2{=}CHCH_2Br$	80	>90 (*R*)
—$(CH_2)_4$—	[a]	**103m**	$CH_2{=}CHCOOCH_3$	63	86 (*S*)
—$(CH_2)_4$—		**104**	$(CH_3)_2SO_4$	59	84 (*S*)
—$(CH_2)_4$—		**104**	$CH_2{=}CHCH_2Br$	71	73 (*R*)
—$(CH_2)_4$—		**105**	$(CH_3)_2SO_4$	65	98 (*S*)
—$(CH_2)_4$—		**105**	CH_3I	57	97 (*S*)
—$(CH_2)_4$—		**105**	$CH_2{=}CHCH_2Br$	75	84 (*R*)
—$(CH_2)_4$—		**105**	*n*-C_3H_7I	70	97 (*S*)
—$(CH_2)_3$—	[b]	**105**	CH_3I	62	94 (*S*)
—$(CH_2)_4$—	[b]	**105**	CH_3I	40	96 (*S*)
H	C_7H_{15}	**103a**	CH_3I	46	47 (*S*)
H	C_2H_5	**103a**	$C_6H_{13}I$	36	42 (*R*)
H	C_2H_5	**103j**	$C_6H_{13}I$	74	42 (*R*)
H	C_2H_5	**103f**	$C_6H_{13}I$	70	52 (*S*)
H	C_7H_{15}	**103d**	CH_3I	48	48 (*S*)
H	CH_3	**103d**	$C_6H_{13}I$	60	51 (*R*)
H	C_7H_{15}	**103e**	CH_3I	75	54 (*S*)

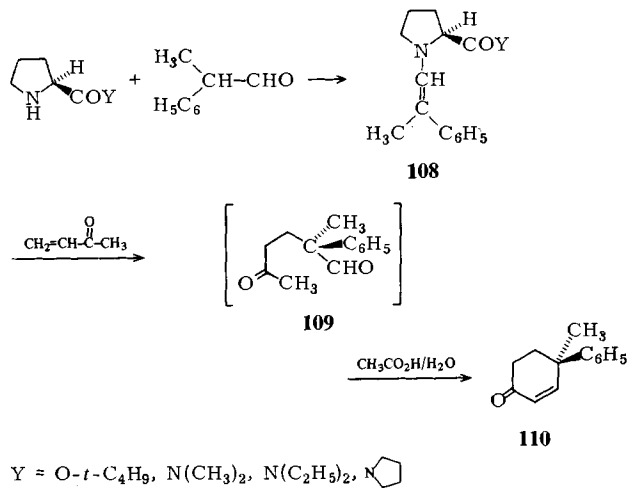
[a] M = Sn. [b] $R^3 = C_6H_5$.

The alkylation of the enamines **106**[121] with allyl bromide gives the 2-allylcyclohexanones **107** in poor yields. Compound **107b** is obtained in a diastereomeric excess of 74%.

The enamine **108** reacts with methyl vinyl ketone to give the 1,5-dicarbonyl compound **109** which, on treatment



with aqueous acetic acid, cyclizes to **110**. Optical yields of up to 49% have been achieved[122, 123].



108

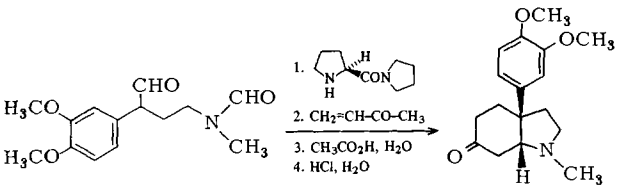
109

110

Y = O-*t*-C_4H_9, $N(CH_3)_2$, $N(C_2H_5)_2$, N⬡

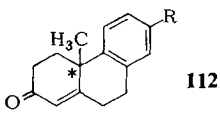
In 1969 *Yamada* reported for the first time the alkylation of enamines **100** (Y = OMe, OEt, O*t*Bu) derived from (*S*)-proline esters (Scheme 1, route A)[124a]. Activated olefins such as acrylonitrile and methyl acrylate, and halides such as allyl bromide and ethyl bromoacetate were used as electrophiles[124]. The enamines **100** react in polar solvents such as alcohols and acetonitrile with acceptable chemical, but poor optical yields. In nonpolar solvents, on the other hand, the reactivity is low, but the enantioselectivity good. Of the proline esters, (*S*)-proline *tert*-butyl ester gives the best optical yields.

This reaction principle has been used successfully for the synthesis of (+)-mesembrine **111**[125, 126].



111

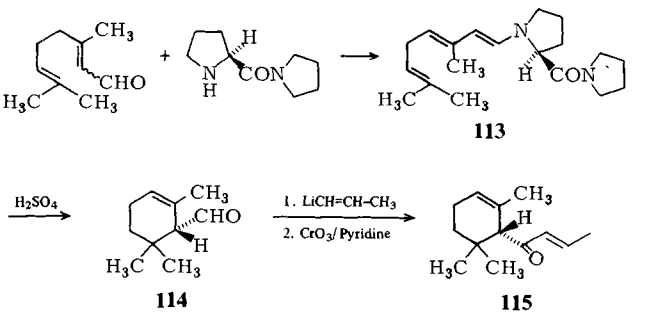
In more extensive investigations, in which the structures of the carbonyl compounds[122, 127] and of the proline derivatives[128] were widely varied, it was possible to raise the optical yields of 4,4-disubstituted cyclohexenones of the type **110** to a maximum of 54%. The reactivity-selectivity problem could not be overcome.



112

Phenanthrone derivatives **112** have been prepared from **110** and used as important intermediates for the synthesis of optically active diterpenes and steroids such as podocarpic acid[129], (*R*)- and (*S*)-$\Delta^{1,9}$-2-octalone[130], or vincamine[131].

By an acid-catalyzed cyclization of the optically active citralenamine **113** it was possible to obtain, in 33% optical

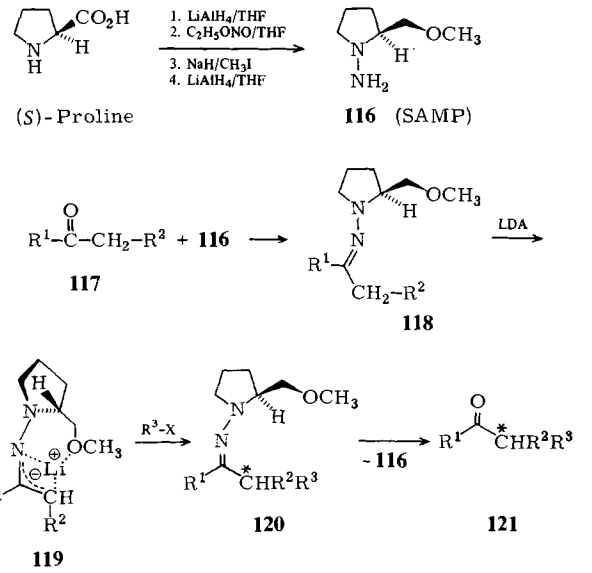


113

114

115

yield, (*R*)-α-cyclocitral **114**, from which (*R*)-(+)-*trans*-α-damascone **115** can be prepared[132].



(*S*)-Proline

116 (SAMP)

117

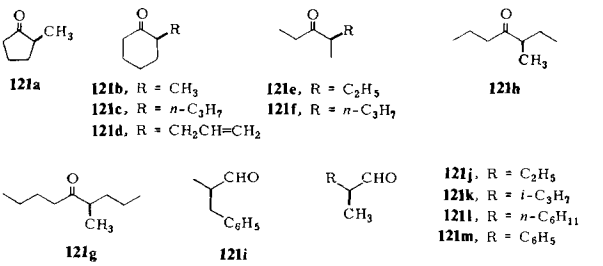
118

119

120

121

Table 7. Ketones and aldehydes **121** prepared by enantioselective alkylation with the chiral auxiliary SAMP **116**. The newly formed C—C bonds are shown by thick lines.



121a

121b, R = CH_3
121c, R = *n*-C_3H_7
121d, R = $CH_2CH{=}CH_2$

121e, R = C_2H_5
121f, R = *n*-C_3H_7

121h

121g

121i

121j, R = C_2H_5
121k, R = *i*-C_3H_7
121l, R = *n*-C_6H_{11}
121m, R = C_6H_5

121	Yield [%] Chemical [a]	Optical	(Configuration)	Ref.
a	66	86	(*R*)	[135]
b	70	99	(*R*)	[135]
c	73	≈86	(*R*)	[135]
d	60	73	(*S*)	[135]
e	61	94	(*S*)	[138]
f	60	99.5	(*S*)	[138]
g	55	≥98	(*R*)	[138]
h	54	≥98	(*R*)	[138]
i	61	82	(*S*)	[134, 135]
j	65	62	(*R*)	[134, 135]
j	71	77	(*S*)	[135]
k	60	57	(*R*)	[134, 135]
l	61	86	(*R*)	[134, 135]
m	80	31	(*R*)	[134, 135]

[a] Total yield from the alkylation.

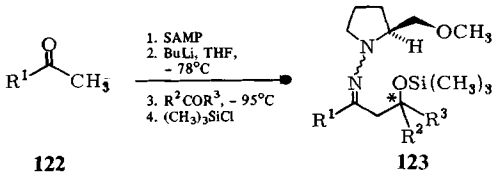
In 1976 *Enders et al.*[133] introduced a new chiral auxiliary, namely (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) **116**, which can be easily prepared from (*S*)-proline. Aldehydes and ketones react with SAMP **116** to give the hydrazones **118**, which can be alkylated asymmetrically in the α-position[133,134].

Lithiation[135,138] of the SAMP hydrazones **118**, which are formed in high yields, leads to the chelate complexes **119**, which have (Z_{CN},E_{CC})-configurations, as has been demonstrated by ^{1}H- and ^{13}C-NMR studies[136,137].

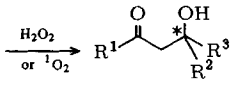
The liberation of the alkylated carbonyl compounds **121** from **120** with regeneration of **116** was carried out either with ozone at low temperatures or hydrolytically after methylation (Table 7).

(*S*)-(+)-4-Methyl-3-heptanone **121f**, the main alarm pheromone of the leaf-cutting ant *Atta texana*, could be synthesized almost enantiospecifically.

Regiospecific and enantioselective aldol reactions were also performed with SAMP **116**[139]. The lithiated hydrazones obtained from ketones **122** were alkylated with carbonyl compounds and the adducts then treated with chloro(trimethyl)silane; the resulting trimethylsilyl ethers **123** were finally oxidatively hydrolyzed to the chiral β-hydroxyketones **124** (*ee* = 31–62%).

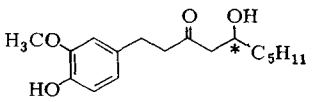


122 **123**



124

This method was used in the asymmetric synthesis of (−)-(*R*)- and (+)-(*S*)-gingerol **125**, the main flavor component of ginger, from acetone, vanillin, and hexanal in an optical yield of 36–39%[140].

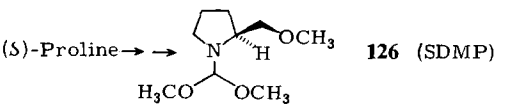


125

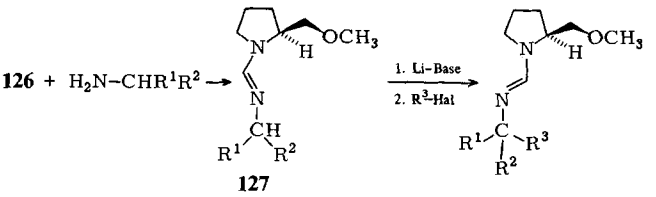
Enders and *Lotter*[141] recently reported a less stereoselective synthesis of α-hydroxyketones and vicinal diols using (*S*)-1-formyl-2-methoxymethylpyrrolidine. *Kolb* and *Barth*[142] employed the (*S*)-proline derivative (−)-(*S*)-1-dimethoxymethyl-2-methoxymethylpyrrolidine (SDMP) **126** as auxiliary chiral agent. The metalation of the amidines **127** leads to azaallyl anions homologous with **119** which, after alkylation, give α-substituted optically active amines or amino acids **128**.

Alkylation of Enolates: Chiral carboxylic acid esters or amides **129** can be converted by metalation into their enolates **130** which, after alkylation and hydrolysis, yield optically active α-alkylcarboxylic acids **131**.

Chiral α-alkylcarboxylic acids **131** have been synthesized by metalation and alkylation of chiral oxazolines[143] and ephedrinamides[144]. Optical induction is at its highest



126 (SDMP)



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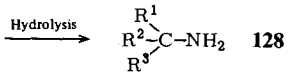
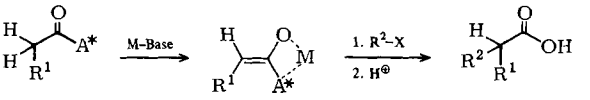


128

R^1 = H, CH_3; R^2 = C≡CH, CO_2H; R^3 = Benzyl, Alkyl

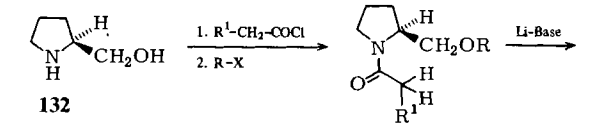
when the second chelate-forming substituent in the chiral auxiliary is a methoxy group. Two papers appearing almost simultaneously described the preparation of optically



129 **130** **131**

M = Li, Mg, B, Al, Zr
A* = Chiral moiety OR* or NHR*

active α-alkylcarboxylic acids by the asymmetric alkylation of chiral amide enolates **133** derived from (*S*)-prolinol **132**[145].



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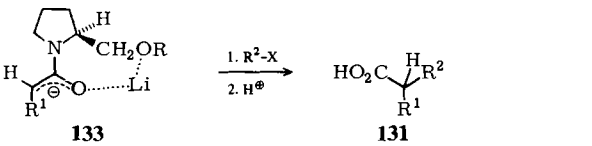
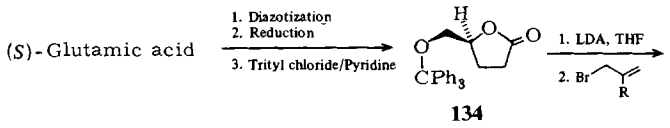


133 **131**

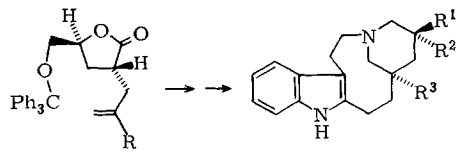
R^1 = CH_3, C_2H_5;
R^2 = CH_3, C_2H_5, *n*-C_4H_9, *i*-C_4H_9, $C_6H_5CH_2$, CH_2=$CHCH_2$

The carboxylic acids **131** were obtained in chemical yields of 78–96% and optical yields of 69–95%[145]. Methylation of the monoanion **133** (R = CH_3) gave the (*S*)-configuration of the α-alkylcarboxylic acids **131**, while the same reaction of the dianion **133** (R = Li) gave the (*R*)-configuration.

The chiral lactone alcohol derivative **134**[146], which can be readily prepared from (*S*)-glutamic acid, can be alkylated—with self-induction—to give the optically active 3-substituted lactone alcohols **135**, which are intermediates in the synthesis of the Pandaca alkaloids (+)-quebrachamine **136**, (−)-velbanamine **137**, and (+)-isovelbanamine **138**[147].

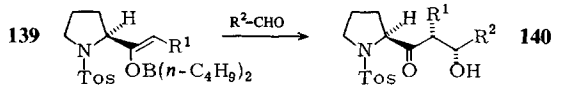


134



135 **136**, $R^1 = R^2 = H$; $R^3 = C_2H_5$
137, $R^1 = C_2H_5$; $R^2 = OH$; $R^3 = H$
138, $R^1 = OH$; $R^2 = C_2H_5$; $R^3 = H$

Evans et al.[148] achieved an enantioselective aldol condensation in optical yields of up to 97% on using the boryl enolates **139** prepared from (*S*)-proline. The corresponding reactions with lithium enolates gave lower optical yields.

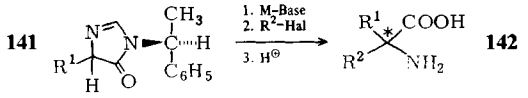


R^1 = H, CH_3; R^2 = C_6H_5, *i*-C_3H_7

Meyers and *Yamamoto*[149] recently reported enantioselective aldol reactions of high *threo*- or *erythro*-selectivity with the use of boryl azaenolates.

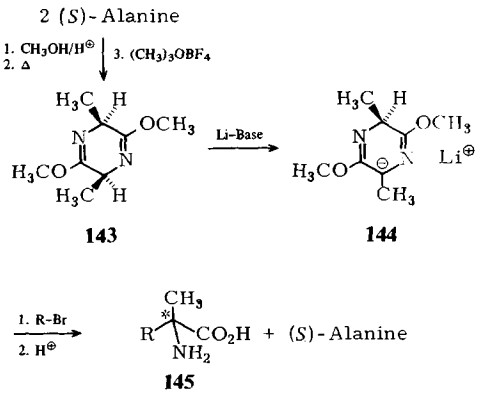
α-Alkylations of α-Amino Acid Derivatives: Because of the high biological activity of some representatives, α-alkyl-α-amino acids have recently attracted a great deal of interest.

Schöllkopf et al. synthesized α-alkyl-α-amino acids **142** by the alkylation of 1-chiral-substituted 2-imidazolin-5-ones **141**, which can be prepared from (*S*)-phenylethyl-



R^1 = CH_3, C_2H_5, *n*-C_3H_7, *i*-C_3H_7, *n*-C_4H_9, $CH_2CH{=}CH_2$, CH_2–Aryl;
R^2 = CH_3, *i*-C_3H_7, *n*-C_4H_9, $CH_2CH{=}CH_2$, $CH_2CO_2C_2H_5$, CH_2–Aryl

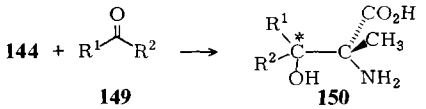
amides of α-amino acids and orthoformic esters. The optical yields of **142** are in many cases greater than 95%.



R = *i*-C_3H_7, $CH_2CH{=}CH_2$, CH_2–Aryl, $C(OH)(C_6H_5)_2$

A further development of this method is the base-induced alkylation of the lactim ether of cyclo-(*S*)-Ala-(*S*)-Ala **143**, which provides, after hydrolysis, the α-methyl-α-amino acids **145** (*ee* = 90—93%)[151].

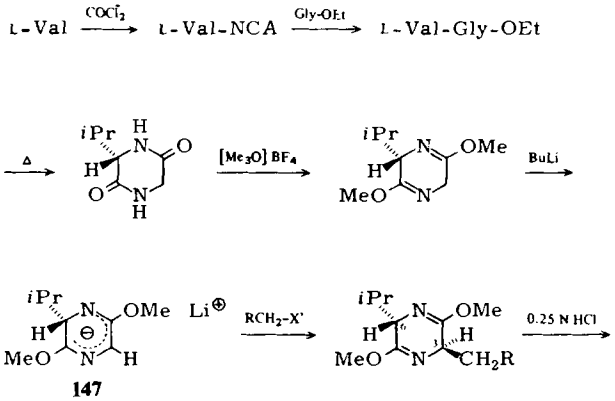
If the lithiated lactim ether **144** is reacted with carbonyl compounds **149** in an aldol condensation with subsequent hydrolysis, chiral α-methylserines **150** are formed with high optical yields. With aldehydes and unsymmetric ketones an additional chiral center appears in the β-position of the serines, albeit with lower induction[153].

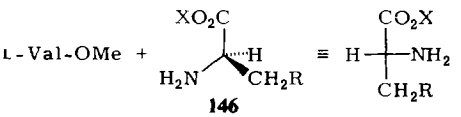


R^1 = H, CH_3, C_6H_5, 4-CH_3O–C_6H_4; R^2 = H, CH_3, C_6H_5

Starting from (*S*)-valine, *Schöllkopf et al.*[152] were able to synthesize a series of β-alkylated (*R*)-alanine derivatives **146** in high chemical and optical yields.

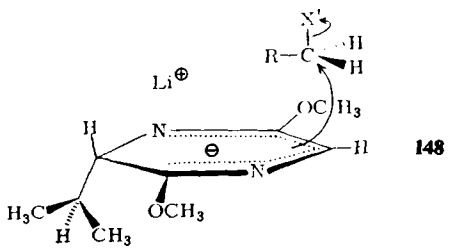
To explain the induction of asymmetry, the above mentioned authors[152] assumed that the lithium compound **147** contains a planar dihydropyrazine anion in which one diastereotopic side is quite effectively screened by the iso-





NCA = *N*-Carboxyanhydride, X = CH_3, H

R = C_6H_5, 3,4-$(OCH_3)_2C_6H_3$, $CH{=}CHC_6H_5$, $-C{\equiv}C-C_6H_5$, $C{\equiv}CH$, $(CH_2)_5CH_3$, 2-Naphthyl-

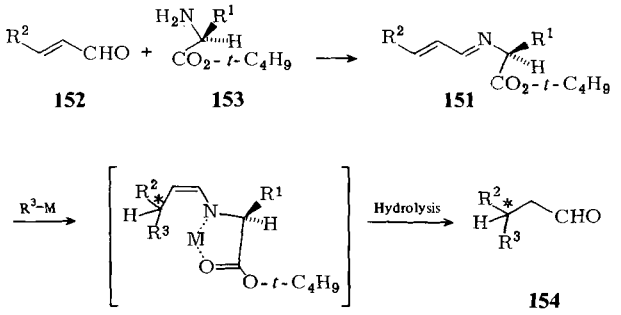


propyl group. The structure **148** is postulated for the more favorable of the two transition states.

3.2.3. Reactions at the β-Carbon Atom of Carbonyl Groups

Michael-Additions: The most important application of this type of reaction is CC bond formation β to a carbonyl function by the addition of carbanions to α,β-unsaturated carbonyl compounds, which are readily accessible *via* aldol or ester condensations. Asymmetric Michael additions have also been known for some time. Thus, as long ago as 1973 a synthesis of (*R*)-3-phenylbutyric acid was presented in which the decisive step is the asymmetric Michael addition of diethyl malonate to an optically active vinyl sulfoxide[154]. On addition of β-dicarbonyl compounds, α-nitrosulfones, and α-nitro esters to methyl vinyl ketone in the presence of catalytic amounts of the alkaloid (−)-quinine enantiomeric excesses of up to 68% were achieved[155]. *Meyers* and *Whitten* synthesized 3-substituted alkanecarboxylic acids, mostly in over 90% optical yield, by addition of organolithium reagents to chiral oxazolines[156]. *Mukaiyama et al.*[157] obtained 3-substituted alkanecarboxylic acids, in some cases with almost quantitative optical purity, by the addition of Grignard reagents or lithium dialkylcuprates to chiral 1,4-oxazepine-5,7-diones.

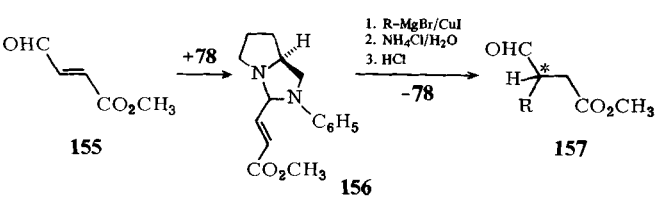
The first asymmetric Michael addition with amino acid derivatives was carried out by *Koga et al.*[158]. They obtained aldehydes **154** (*ee* ≤ 98%, yield *ca.* 50%) substituted in the 3-position by the 1,4-addition of carbanions to chiral, α-β-unsaturated aldimines **151** prepared from α,β-unsaturated aldehydes **152** and α-amino acid *tert*-butyl esters **153**. This method has also been used for the preparation of 2-substituted cycloalkane-[159a] and 1-methylcycloalkanecarbaldehydes[159b] (*ee* = 82–93%).



152 **153** **151** **154**

M = K, Mg
R^1 = *i*-C_3H_9, *i*-C_4H_9, *t*-C_4H_9; R^2 = CH_3, C_6H_5 ;
R^3 = C_2H_5, *n*-C_4H_9, *cyclo*-C_6H_{11}, $CH(CO_2C_2H_5)_2$, C_6H_5, $(CH_3)_2C{=}CH(CH_2)_2$

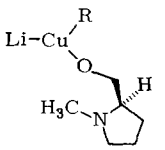
Mukaiyama et al.[160] were able to react (*S*)-2-anilinomethylpyrrolidine **78** with methyl 3-formylacrylate **155** to give the chiral aminals **156**. These react with Grignard compounds to give high optical yields of the methyl 3-alkyl-3-formylpropionates **157** (*ee* ≤ 93%).



155 **156** **157**

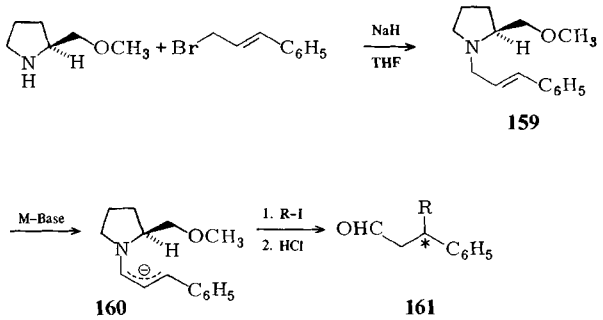
R = C_2H_5, *n*-C_3H_7, *i*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, $C_6H_5CH_2$

In the reversed mode of operation, addition of chiral organocuprates of type **158** to achiral α,β-unsaturated carbonyl compounds, lower optical yields were obtained. Thus, in the reactions of 2-cyclohexenone and of 4-phenylbut-3-en-2-one with **158** (R = *n*-C_4H_9), optical yields of 5 and 15%, respectively, were obtained[161]. Methylation of 1,3-diphenyl-2-propen-1-one with **158** (R = CH_3) gave (*S*)-1,3-diphenyl-1-butanone (*ee* = 68%)[162].



158

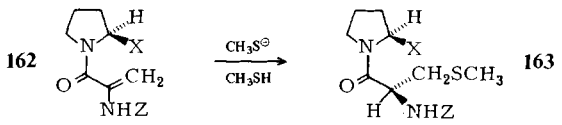
Ahlbrecht and *Enders et al.*[163] metalated the chiral allylamines **159**; the resulting chiral homoenolates **160** were then alkylated. Subsequent hydrolysis furnished the β-substituted aldehydes **161** (*ee* = 64–67%).



159 **160** **161**

R = CH_3, C_2H_5, *i*-C_3H_7

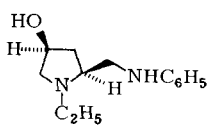
Aside from C-nucleophiles, other nucleophiles can also be added asymmetrically to α,β-unsaturated carbonyl compounds. While attempting the biomimetic formation of cysteine, *Schmidt et al.*[164] added thiolates to *N*-protected chiral α-aminoacrylic acid derivatives **162** (dehydropeptides). The optical yields of **163** were up to 90%.



162 **163**

X = $CONHCH_3$, $CONH_2$, $CON(CH_3)_2$; Z = $C_6H_5CH_2OCO$

An analogous asymmetric addition of thiolates to 2-cyclohexenone induced by catalytic amounts of the (*S*)-4-hydroxyproline derivative **164** has recently been described[165].

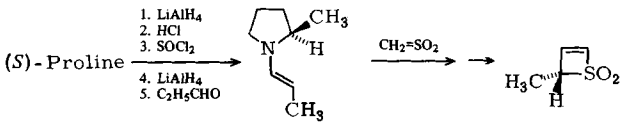


164

An asymmetric Michael addition has been described by *Kishi et al.* in the enantioselective total synthesis of the bacteriostatic gliotoxin[166].

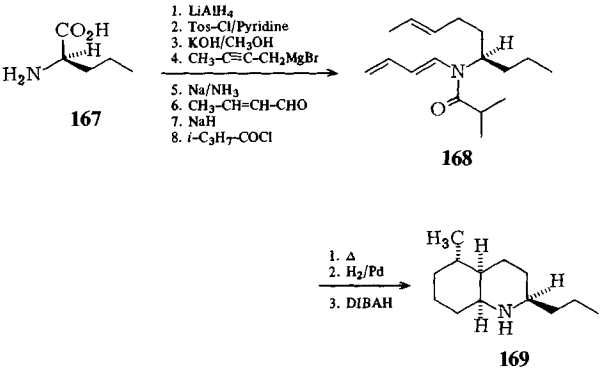
3.2.4. Cycloadditions

Synchronous cycloadditions, which show a high regioselectivity, are also enantio- or stereoselective if one of the reaction partners is chiral. *Paquette et al.*[167] obtained (*R*)-(−)-4-methylthiete *S,S*-dioxide **166** in 25% optical yield in the [2+2]-cycloaddition of thioformaldehyde *S,S*-dioxide to the enamine **165**.



165 **166**

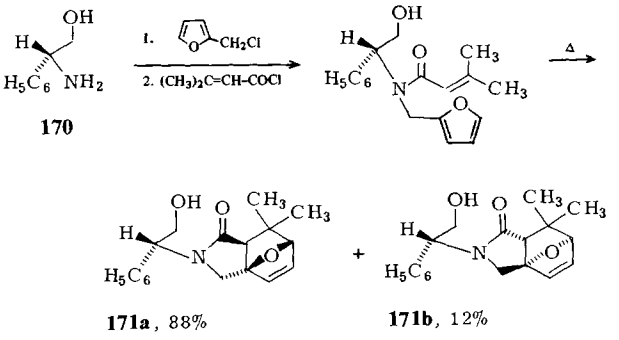
Asymmetric Diels-Alder reactions have been performed with variable success[168]. Especially high optical induction can be obtained in the intramolecular Diels-Alder reactions of chiral molecules. (2*R*)-Pumiliotoxin C **169** has been prepared from (*R*)-norvaline **167** (*ee* = 97%). Here the asymmetric center of the triene **168** controls the configuration at three carbon atoms[169].



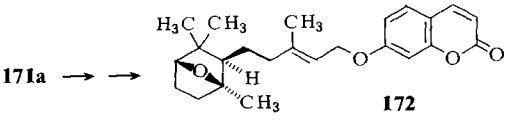
167 **168** **169**

Asymmetric Diels-Alder reactions also play a decisive role in the synthesis of cytochalasins. The primary chiral information is carried by (*S*)-alanine and (*S*)-phenylalanine in this case[170].

Mukaiyama et al.[171] have reported the total synthesis of the sesquiterpene (+)-farnesiferol C **172**, starting from (*R*)-phenylglycinol **170**. The key step of this synthesis is likewise an intramolecular Diels-Alder reaction with high asymmetric induction. In this case the two cycloadducts **171** are formed in a diastereomeric ratio of 88 : 12.



170 **171a**, 88% **171b**, 12%

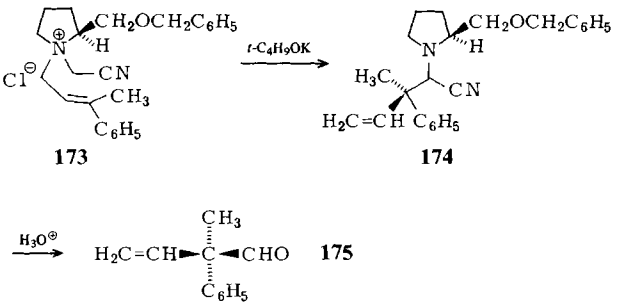


172

Danishefsky et al.[172] have succeeded in synthesizing pretyrosine, the biosynthetic precursor of (*S*)-tyrosine, by a [4+2]-cycloaddition using an (*S*)-pyroglutamic acid derivative. *Grigg* and *Kemp et al.*[173] have reported an asymmetric variation of a 1,3-dipolar cycloaddition in which phenylglycine was used as the source of the chiral information.

3.2.5. [2,3]-Sigmatropic Rearrangements *via* Chiral Ammonium Ylides

The asymmetric [2,3]-sigmatropic rearrangement of (*S*)-(*E*)-**173**, a derivative of (*S*)-proline, gave the (*E*)-aminonitrile **174**, which was saponified to (+)-2-methyl-2-phenyl-3-butenal **175** (*ee* = 90%)[174]. If the benzyloxymethyl moiety in **173** is replaced by a methyl group, the optical yield of the chiral aldehyde **175** falls drastically[174].



173 **174** **175**

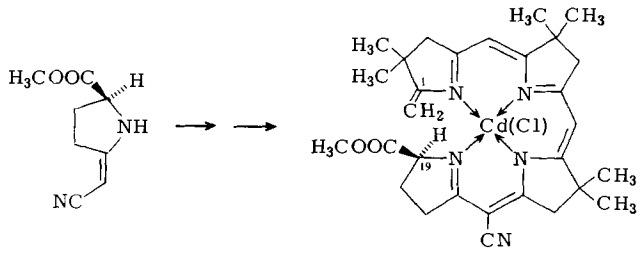
3.2.6. β-Lactam Syntheses

The stereoselective synthesis of β-lactams, particularly penicillins and cephalosporins, has been intensively investigated for many years because of the great pharmacological importance of these substances. A detailed discussion of the numerous β-lactam syntheses in which the induction of asymmetry by chiral amino acids plays a role would be beyond the scope of this contribution. Therefore, the reader is referred to reviews[175, 176] and the more recent original publications[177] specifically dealing with this topic.

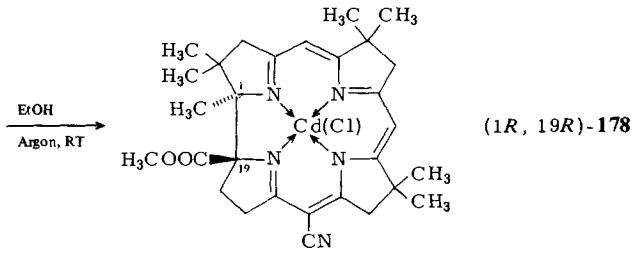
3.2.7. Photochemical Cyclization

In investigations on the biosynthesis of corrinoids the central theme is the nature of the ring-closure reaction by means of which the characteristic direct coupling of rings A and D in the corrin ligand takes place. *Eschenmoser et al.*[178] have shown that a transformation from the porphyrinogen structure type to that of the corrins can occur without the participation of an external reducing agent.

The synthesis of the corrinate **178** starts from the (*S*)-pyroglutamic acid derivative **176**; the key reaction is a photochemically induced A/D-secocorrin→corrin cycloisomerization of the secocorrinate **177**. No optical yield is reported. A comparison of the spectrum with the spectra of natural corrinoids leaves no doubt of the (*R*)-configuration at C-19.



176 (19S)-177

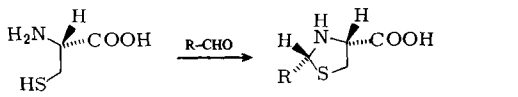


(1R, 19R)-178

3.3. Other Reactions Taking Place with the Transfer of Asymmetry

3.3.1. Stereoselective Addition of NH- and SH-Compounds to Carbonyl Groups

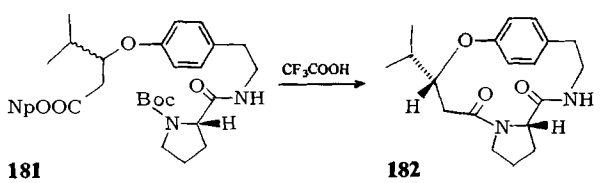
The vitamin (+)-biotin has been synthesized from naturally occurring hexoses[179] or pentoses[179] or from (*R*)-cysteine **179**. When **179** is used as starting material, it is first condensed with benzaldehyde to give the sterically pure product **180a** in almost quantitative yield. Reaction of **179** with 4-methylbenzaldehyde also occurs stereospecifically to yield **180b**[181]. These results are consistent with the configuration found previously for the thiazolidines formed from (*S*)-penicillamine and various aldehydes[182].



179

180a, R = C_6H_5
180b, R = 4-CH_3-C_6H_4

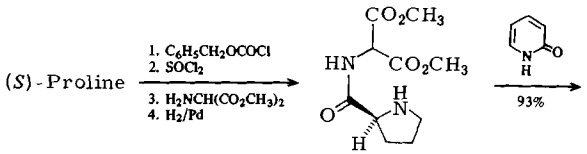
The particular suitability of proline as a carrier of chiral information to other centers of complex molecules will be outlined on the basis of three examples[183]. In the peptide cyclization of **181**, the peptide **182** is obtained with high stereoselectivity by the intramolecular optical induction of the (*S*)-proline moiety[183a].



181 **182**

Np = *p*-NO_2-C_6H_4
Boc = *t*-C_4H_9O-CO

In the asymmetric total synthesis of brevianamide E **183** *Kametani et al.*[183] started from natural (*S*)-proline. An important step in this synthesis was the stereospecific cyclization of **184** with the formation of the diketopiperazine **185**.



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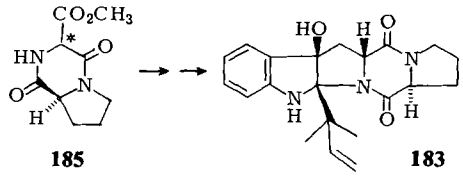
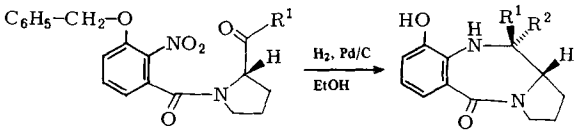


185 **183**

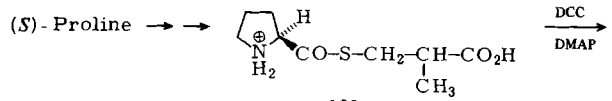
Excellent stereoselectivity was observed by *Mohr*[183c] for the cyclization of the (*S*)-proline derivative **186** to the benzodiazepine system **187**. The cyclization occurs after hydrogenation of the nitro-group to an amine.



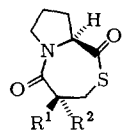
186, R^1 = 3-Indolyl

187a, R^1 = H; R^2 = 3-Indolyl(92%)
187b, R^1 = 3-Indolyl; R^2 = H(8%)

The thiol ester **188** cyclizes upon treatment with dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dichloromethane at room temperature to a mixture of the diastereomeric bicyclic compounds **189a** and **189b** (7:3)[184]. Compound **189a** could acquire pharmacological importance as an antihypertensive agent.



188



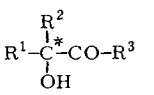
189a, R^1 = CH_3, R^2 = H
189b, R^1 = H, R^2 = CH_3

Shin et al. recently reported on the stereoselective addition of chiral α-amino acids to β,β-dibromo-α-imino acids[185].

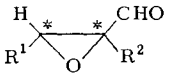
3.3.2. Asymmetric Halolactonization

An asymmetric variation of the well-known halolactonization reaction[187] has recently been reported by *Terashima et al.*[186]. This new, highly stereoselective synthesis permits the preparation of intermediates for chiral α,α-disubstituted α-hydroxycarboxylic acids **190**[186c], α-hydroxyketones **191**[186c], and functionalized epoxides **192**[186d].

The source of the chiral information is consistently amino acids. Particularly high stereoselectivity has been found with the use of chiral proline.

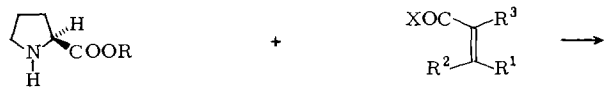


190, R^1, R^2 = Alkyl or Aryl
R^3 = OH
191, R^1, R^2 R^3 = Alkyl or Aryl



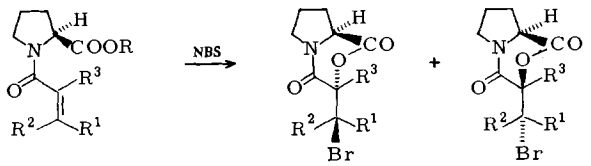
192, R^1, R^2 = Alkyl or Aryl

The reactions of (*S*)-proline or (*S*)-proline ethyl ester with appropriately substituted acrylic acids **193a** or acrylic acid chlorides **193b** yield α,β-unsaturated *N*-acyl-(*S*)-prolines **194**. The halolactonization of **194** with *N*-bromosuccinimide (NBS) leads to formation of a mixture of diastereomeric lactones **195** and **196**, **195** being formed preferentially (*de* > 90%)[186].



(*S*)-Proline, R = H
(*S*)-Prolineethyl ester, R = C_2H_5

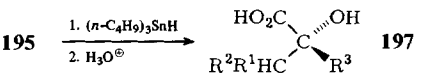
193a, X = OH
193b, X = Cl



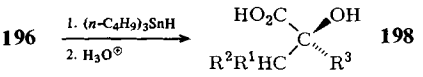
194 **195** **196**

R^1 = H, CH_3, n-C_6H_{13}, C_6H_5; R^2 = H, CH_3; R^3 = CH_3

The intramolecular transfer of the asymmetry of the chiral center of (*S*)-proline to the new asymmetric center in **195** or **196** proceeds *via* a bromonium ion[186c]. Debromination[188] of **195** and **196** with tri-*n*-butyltin hydride followed by hydrolysis leads to the chiral α-hydroxycarboxylic acids **197** and **198**, respectively, and (*S*)-proline.



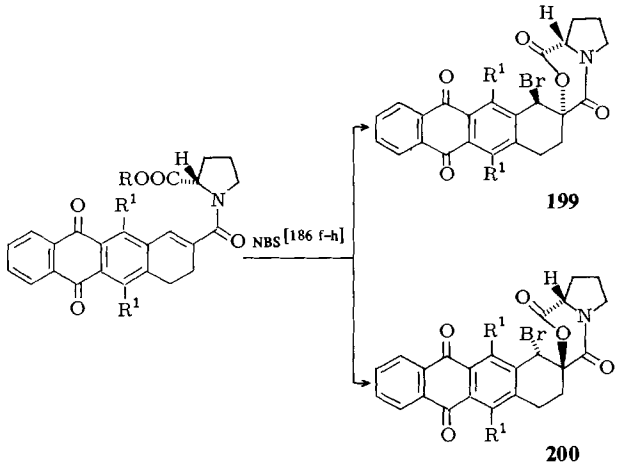
195 **197**



196 **198**

When a mixture of the diastereomers **195** and **196** was converted into the epoxide **192** with simultaneous reductive removal of the (*S*)-proline function, **192** was obtained in optically active form[186d].

One particularly interesting aspect is the application of the (*S*)-proline-induced asymmetric halolactonization to the stereoselective synthesis of some anthracycline antibiotics. The bromolactones **199** and **200** are formed in the ratio 96:4[186g]. If the (*S*)-proline in the α,β-unsaturated *N*-acyl-(*S*)-prolines **194** is replaced by other amino acids such as (*S*)-phenylalanine, *N*-benzyl-(*S*)-phenylalanine, or 1,2,3,4-tetrahydroisoquinoline-3-(*S*)-carboxylic acid, the induction of asymmetry in the halolactonization is smaller, or no lactone at all is produced[186c,e].



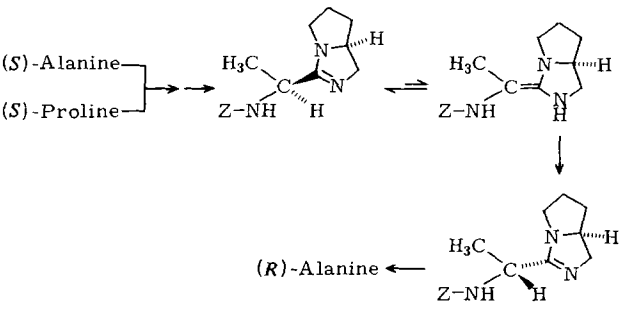
199

200

R = H, C_2H_5; R^1 = H, OH, OCH_3

3.3.3. Equilibration and Stereoselective Protonation

Imidazolines **201**, prepared from (*S*)-alanine and (*S*)-proline, gave (*R*)-alanine on hydrolysis. This can be best explained in terms of epimerization and stereoselective protonation with induction by the chiral center originating from (*S*)-proline[189].



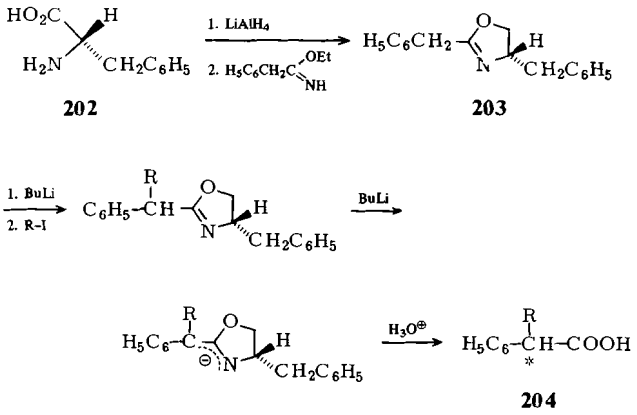
Z = $C_6H_5CH_2OCO$ **201**

The (*R*)-analine was obtained in an optical yield of up to 94%[189]. Nonnatural (*R*)-analine can, of course, also be obtained from racemic alanine in this way.

In the synthesis of chiral 2-phenylalkanecarboxylic acids **204** *via* chiral oxazolines **203**, (*S*)-phenylalanine **202** was used as the source of the chiral information[190].

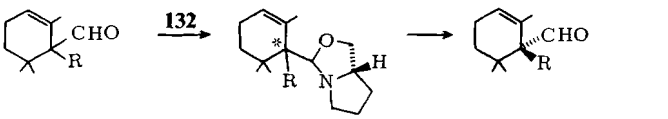
The carboxylic acids **204** were obtained in optical yields of up to 53%[190]. More effective than this is the asymmetric alkylation of chiral amide enolates based on (*S*)-prolinol **132**[145].

The chiral oxazolidine derivative **205a**, prepared from racemic cyclocitral **206a** and (*S*)-prolinol **132** in the presence of catalytic amounts of *p*-toluenesulfonic acid, gave, upon acid hydrolysis, (*R*)-cyclocitral (*S*)-**206a** in 19% optical purity[191].



R = CH_3, C_2H_5, *i*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}

Analogously, (*S*)-6-hydroxycyclocitral (*R*)-**206c** has been obtained from racemic 6-benzoyloxycyclocitral **206b** (*ee* = 63%)[191].

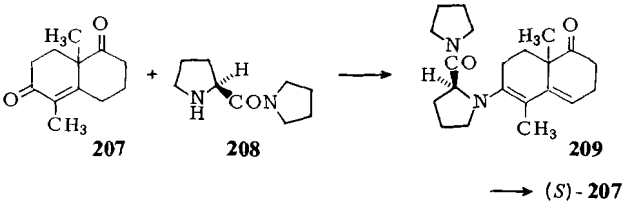


(*R*,*S*)-**206a**, R = H
(*R*,*S*)-**206b**, R = $OCOC_6H_5$

205a, R = H
205b, R = OH

(*R*)-**206a**, R = H
(*S*)-**206b**, R = OH

By heating the racemic dicarbonyl compound **207** with an equimolar amount of (*S*)-proline pyrrolidide **208**, the dienamine **209** was obtained, which, upon hydrolysis with hydrochloric acid, gave the diketone **207** in the (*S*)-configuration (*ee* ≤ 63%)[192].



207 **208** **209**

→ (*S*)-**207**

3.3.4. Stereoselective Acylation of Cyclic *meso*-Diols

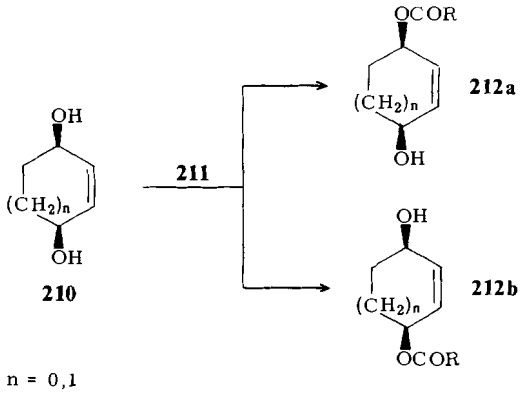
In the reaction of cyclic *meso*-1,3-diols **210** with *N*-protected phenylalanyl chlorides **211**, *Yamada et al.*[193] observed the preferential formation of one of the two possible diastereomeric monoesters **212**.

The stereoselectivity of the above acylation is not particularly good. The monoesters **212** partially ring-substituted by alkyl groups have been used for the synthesis of optically pure steroids[194] and prostaglandins[195].

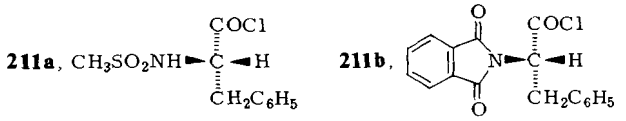
3.3.5. Stereoselective Epoxidation

A key reaction in the stereoselective total synthesis of dendrobatide toxin 251 D is the epoxidation of the (*S*)-proline derivative **213**, which is accomplished with a diastereomeric excess of more than 80%.

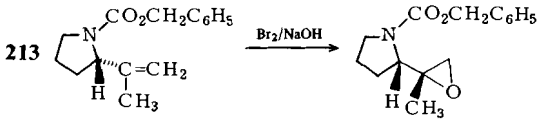
In the epoxidation of **213** with *m*-chloroperbenzoic acid no diastereoselectivity was observed[196b]. The stereoselective epoxidation of (*S*)-*N*-tosyl-3,4-dehydroproline with



n = 0,1



trifluoroperacetic acid has been investigated by *Kahl* and *Wieland*[197].



3.3.6. Synthesis of Chiral Phosphorus Compounds

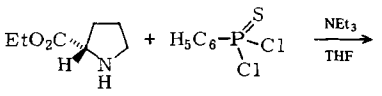
A series of chiral organophosphorus compounds **214** has been synthesized by *Koizumi et al.*[198], whereby amino acids were used as the source of the chiral information.

R^1 = CH_3, C_6H_5, OC_6H_5; R^2 = C_2H_5, *n*-C_4H_9, C_6H_5, OC_6H_5;
R^3 = CH_3, C_2H_5, *n*-C_3H_7, *i*-C_3H_7

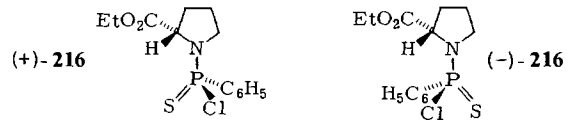
The authors do not give the absolute configurations for either the educts or **214**, but of the two chromatographically separable diastereomeric educts one is always formed preferentially because of the influence of the chiral center of the (*S*)-proline ethyl ester. The chiral, practically enantiomerically pure organophosphorus compounds **214** are obtained from the pure diastereomers by acid alcoholysis.

The reaction of phenylphosphonothioic dichloride **215a** with (*S*)-proline ethyl ester in THF/triethylamine at room temperature leads to a mixture of diastereomeric monochlorides **216** in 90% yield[198d]. After chromatographic separation, 48% of (+)-**216** and only 5% of (−)-**216** is isolated[198d].

Starting from (+)-**216**[198d], a series of optically active phosphorus(v) compounds could be synthesized by substitution of the chlorine atom attached to the phosphorus with OC_6H_5, OCH_3, and NH_2 groups. Walden inversion takes place in every case. By treatment with *m*-chloroper-



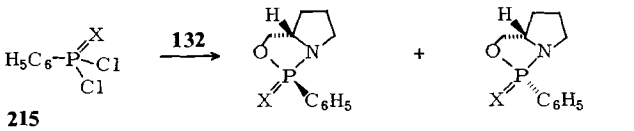
(*S*)-Proline ethyl ester **215a**



(+)-**216** (−)-**216**

benzoic acid the sulfur can be replaced by an oxygen atom with retention of optical activity. Finally, by acid alcoholysis the pyrrolidine moiety can be replaced by an alkoxy residue.

Koizumi et al.[198e] observed a remarkable diastereoselectivity in the reaction of (*S*)-prolinol **132** with **215a**. The absolute configuration of the resulting diastereomeric bicyclic compounds **217a** and **218a** was determined by NMR spectroscopy. The diastereoselectivity in the reaction of (*S*)-prolinol with **215a** was lower than that observed with the isoelectronic oxygen compound **215b**.



215

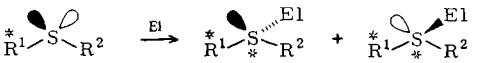
a, X = S; **b**, X = O

217a (35–45%) **218a** (40–45%)
217b (40–60%) **218b** (10–35%)

From the diastereomers **217** and **218**, which can be separated chromatographically[198g], numerous enantiomerically pure phosphorus(V) compounds were synthesized[198f,g]. In particular the base-catalyzed methanolysis as well as reactions with Grignard reagents were investigated.

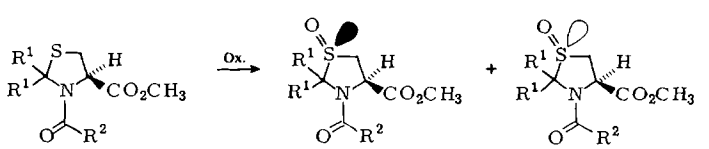
3.3.7. Synthesis of Chiral Sulfur Compounds

In the reactions of optically active sulfides asymmetry is produced in the *S*-substituted diastereomeric compounds formed[199].



El = Electrophile

Optically active cysteine and methionine derivatives could be oxidized, with asymmetric induction, to the sulfoxides. Thus, (*S*)-methionine reacts stereospecifically with H_2O_2[200a] or gold(III) compounds[200b] to give the (*S,S*)-methionine *S*-oxide. In the oxidation of the chiral thiazolidine-4-carboxylic acid methyl esters **219** the diastereomeric sulfoxides **220a** and **220b** are formed (1 : 1.5)[201].



219 **220a** (60%) **220b** (40%)

R^1 = H, CH_3; R^2 = CH_3, C_6H_5

3.3.8. Miscellaneous

Recent literature describes a series of further investigations in which the chirality of amino acids or amino acid derivatives is used to prepare optically active natural products. Transfer of the chirality from the amino acids to a newly arising asymmetric center occurs one or more times in the course of these syntheses. Examples of such syntheses of natural products are the preparation of sugars from (*S*)-alanine[202], (*R*)-threonine[203], or (*S*)-glutamic acid[204], and syntheses of alkaloids[205], terpenes[206] and peptide derivatives[207].

Optically active micellar systems have been used to influence the stereochemical course of reactions through the formation of micelles. In particular, control of the hydrolysis reactions of racemic esters by chiral micellar structures based on histidine, phenylalanine, alanine and cysteine has been investigated[208].

4. Concluding Remarks

Nature provides us with a wide range of optically active natural compounds ("chiral pool"); these can be used as substrates in stereoselective syntheses. Particularly frequent use is made here of sugars and naturally occurring hydroxycarboxylic acids such as tartaric acid and malic acid. In recent years, however, increasing use has been made of amino acids as educts in asymmetric syntheses. The reasons for this lie in the great structural variety and ready availability of this class of compounds. Particularly attractive here is that—other than in the case of sugars and hydroxycarboxylic acids—usually both optical antipodes are industrially available.

Strikingly high selectivities have been achieved in asymmetric syntheses with proline or proline derivatives, probably because of the rigidity of the five-membered ring.

The amino acids hitherto used principally for peptide syntheses will in future become the subject of ever-increasing attention as the starting materials for chiral target molecules with widely variable structures. The processes in which achiral precursors are converted with the aid of catalytic amounts of an optically active amino acid into a stereoisomer of the target molecule seem particularly attractive.

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Natural *versus* Indexing Language in Chemical Documentation

By Robert Fugmann*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

In any literature search one must be able to *predict* which modes of expression have been used to represent the concepts of interest in the search file. It is these lingual expressions which will be looked up or will constitute the search parameters in a mechanized search. In the case of *general* concepts and statements, uncontrolled natural language lacks the required representational predictability, as is demonstrated, for example, for classes of chemical compounds and for types of reactions. Hence, considerable loss of relevant information is bound to occur in searches for these concepts in free text files, regardless of how advanced a computer program may be. By restricting the modes of expression as is achieved by means of an indexing language and its reliable employment, predicability is increased and, consequently, information loss is drastically reduced.—In contrast, the modes of expression for *individual* concepts (*e.g.* individual chemical substances, authors, institutions) are, by their very nature, often sufficiently predictable in uncontrolled natural language. In these cases, the value of translating them into indexing-language expressions is often questionable. This holds true in particular if an indexing language does not (yet) provide adequate expressions to represent the concepts, and also in the case of ambiguous natural language expressions. Here, preserving the original, uncontrolled terms in the search file is advisable, at least in addition to an attempted translation into the indexing language.—The weaknesses of uncontrolled natural language files become apparent only at a rather late stage in the continual expansion of an information system. In its early stages the necessity of predictability is reduced through the effectiveness of human memory and the—initially—relatively high homogeneity of the experts' linguistic usage during that short period of time. Furthermore, loss of relevant information as a consequence of the lack of predictability will at first be minimal and will not yet be noticed as a steadily increasing source of search failure. Nor does the steady rise in costs for excogitating and phrasing queries with more and more alternatives become apparent at this stage. It is largely for these reasons that uncontrolled natural language systems have unjustifiably frequently been preferred. The typical weaknesses and strengths of both kinds of language suggest combining them so that their inherent strengths are retained and utilized as far as possible.

1. Introduction

When one sets out for searching the literature relevant to a topic of interest one must excogitate a keyword—or several of them—for this topic. It is hoped that under such a keyword relevant references are listed in an index, or one uses these keywords as search parameters in a mechanized file which comprises the literature of the subject field.

It will always be appreciated by an inquirer if these key-

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words originate from his familiar expert language and when he need not subject himself to restrictions in his lingual usage. This is possible in printed indexes and also in many computerized search files. Any kind of artificial, "indexing-language" mode of expression is felt more cumbersome because it must be learnt beforehand and continually exercised. These expressions are well known in library classification and in certain computerized files as well. Obviously, however, simplicity and convenience are not the only factors to take into consideration when designing or acquiring an information system. Any system should be rejected which does not enable one to attain the goal of sufficiently accurate literature searches, however cheap and simple the system may be.

The necessity or dispensability of indexing or natural language in information systems has often been investigated, but the results and conclusions have been contradictory (cf. *e.g.* [1-23]). Some workers postulate that there is nothing easier and more effective than entering the original texts into the file without any modification. One should be able to answer any conceivable inquiry using such a file, it is argued, because nothing will be lost and nothing will be added, and, moreover, the expensive translation into an indexing language will be circumvented. Other workers hold against the ambiguity of the free lingual usage of the authors, the context-dependence of the meaning of words and the incessant change in their meaning with the course of time. All this impairs the accuracy of the searches in an author-lingual file. Most important, however, unrestricted modes of expression often lack that peculiar property which is crucial if the language is not used for conversation and the mere communication of ideas but instead for the purpose of directed searching through a file of documents: We are dealing here with the *predictability* of the modes of expression for the concepts in the search file[5,6,13,24,25]. It is inherent in indexing languages that they provide this predictability, particularly if they are employed sufficiently reliably. We shall investigate this topic in some detail in the following.

2. The Semantic Triangle

We shall base our considerations on a variant of the "semantic triangle" of *Ogden* and *Richards*[26] (cf. also [27-30]). The corners of the triangle are occupied by the "Referent", the "Concept" and the lingual "Expression" for the concept (Fig. 1).

By "referent" we mean everything about which one can make a meaningful statement[28]. A molecule, for example, is a concrete referent. One can say which atoms are contained in it and how they are connected with each other, and which biological and chemical properties it displays *etc.* An abstract referent is a chemical reaction or a property of matter.

"Concept" is taken as the imagined summarization of all meaningfull statements that can be made on a referent. In other words, the concept is the entirety of the essential features of a referent.

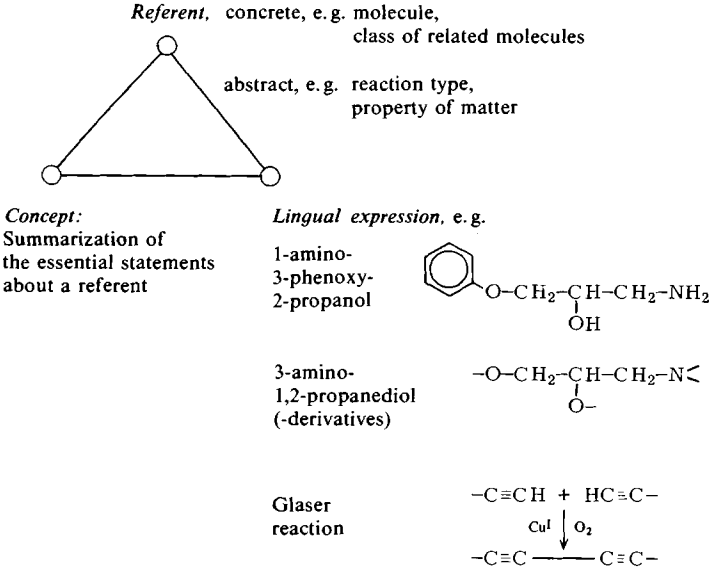


Fig. 1. The semantic triangle.

If we want to talk or write about something imagined we must somehow express the imagined. We must denote it with symbols or the words of our language. We have therefore agreed upon through which symbol, word, or group of words a certain concept is to be expressed. Thus, "Glaser reaction" means a particular way of connecting acetylenic carbon atoms with each other.

Using the semantic triangle we can easily attain certainty on which is the search goal if an inquirer requests information on, *e.g.*, aminopropylene glycol.

Certainly he does not search for the referent itself, *i.e.* for the substance aminopropylene glycol, for in this case he would order the desired amount from a supplier. Besides that, abstract referents, *e.g.* a property of matter or a type of chemical reaction, could not be provided physically to him.

Nor can the expression, which an inquirer happens to have used to describe the topic of his interest, be the real goal of his search. For example, an inquirer may be interested in the Glaser reaction. Then it would be a great misunderstanding on the part of the documentalist if he restricted the search to those documents in which precisely the expression "Glaser reaction" occurs. Much more, any text is relevant in which the *concept* of this reaction is expressed, and in fact independent of the kind of words, sentences, structural formulas *etc.* having been used.

For example, an author may have spoken of the Eglinton, Hay, or Cadiot-Chodkiewicz reaction, or may have avoided any of these names and chosen the reaction equation instead, as shown in Figure 2.

Not only can one and the same concept be expressed differently, but one and the same lingual expression can have different meanings. Thus, the term Cadiot-Chodkiewicz reaction is also used for the coupling of acetylenes with halogenated allenes to yield conjugated enynes (cf. Fig. 2). For many reactions one will encounter a great variety of definitions in the literature.

Hence, it is always the concept which is searched by an inquirer, and not the referent nor the expression of the in-

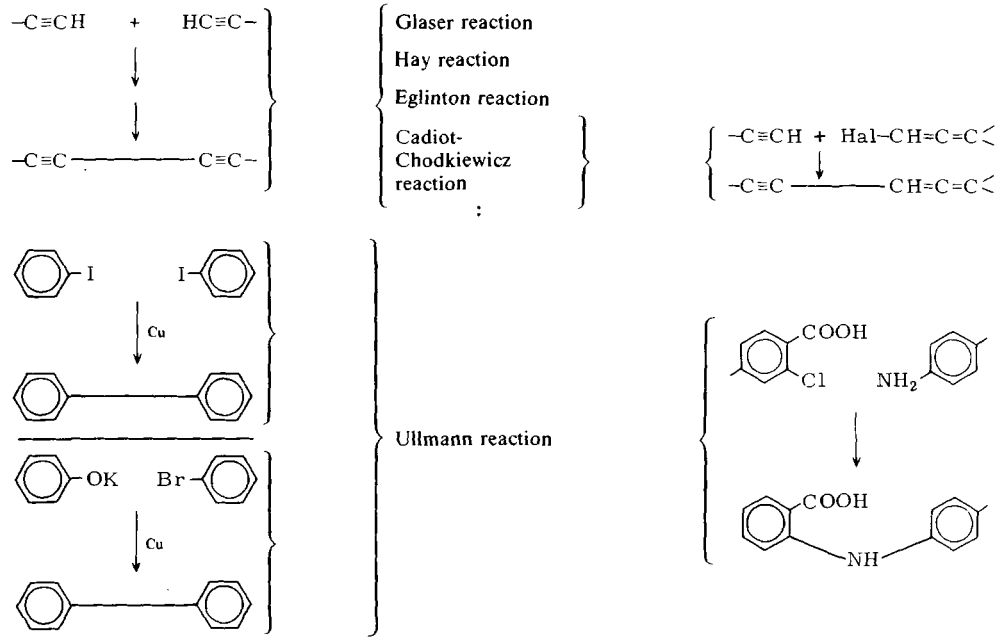


Fig. 2. Ambiguity and multiplicity of natural language expressions.

quirer. The expression only serves as an aid for reaching the search goal, but by no means does it constitute the goal itself. According to these considerations we complete our semantic triangle using the Glaser reaction as an example, and at the same time we introduce an important differentiation between two kinds of lingual expression (see Fig. 3).

3. Lexical *versus* Non-Lexical Mode of Expression

It is conducive to our later discussion to separate the "lexical" expressions from the "non-lexical" ones. A *lexical* expression is deemed one which can unambiguously be entered into and located in a dictionary or lexicon. This holds true for any firmly determined, agreed-upon, linear sequence of alphanumeric symbols with which a concept is expressed, *e.g.* a name for a reaction, a substance, or a person. If for a concept *non-lexical* expressions are in use, for example multi-word phrases of any kind, (such as, *e.g.* expressions of the type of definitions), then the variety of these expressions is very large, often even infinitely large. This is particularly apparent in the case of chemical reactions. This has far-reaching consequences for the retrieval of the concepts expressed in this non-lexical manner (see Sections 3.1 and 3.2).

3.1. Expressions for Reaction Types

For oxidative coupling reactions of acetylenes half a dozen reaction names may have to be taken into consideration, four of which have been entered in Figure 3. This concept may, however, have been expressed in the non-lexical manner as well, namely through typical educts and products in the Glaser reaction. This mode of expression for reactions even markedly dominates in the literature, and in fact for good reasons, which shall, however, not be discussed here in detail. It is essential for our considerations that the number of conceivable, non-lexical expressions for this concept is infinitely large. Their multiplicity corresponds to that of the conceivable individual educts and products in this reaction.

When commencing a literature search for a concept of interest, one must always know in advance how this concept is represented in the search file, for precisely these expressions will have to be adressed by corresponding, alternative search parameters. If one omits only one of the expressions through which the concept of interest is expressed in the search file, then this will inevitably lead to loss of relevant information. All those references in which the omitted expression was used will not be found.

If, now, all the various author-lingual expressions for a reaction were entered into the search file without any restriction, one would have to enumerate as search alternatives in the query all those educts and products through which, *e.g.*, a Glaser reaction might have been expressed in the literature. Since this is impossible, it is correspondingly impossible to perform a literature search anything like completely in a file which has been compiled in this manner.

If there is at least one single name for a reaction of interest, the incompleteness of a search with this name as a parameter is not so conspicuous. One will always find a few references, but which and how many had escaped the search remains hidden.—It is, however, only a very small fraction of reactions for which a name has ever been coined. Hence, the majority of reactions cannot be found at all by names.

It has occasionally been held against these considerations that one need not phrase *any conceivable* author-lingual expression, but only those few which have in fact *entered the file*. The expert could, it is argued, fairly reliably conjecture which specific examples might have been published, and he could therefore restrict his search parameters to just these "practically important" ones. This is how-

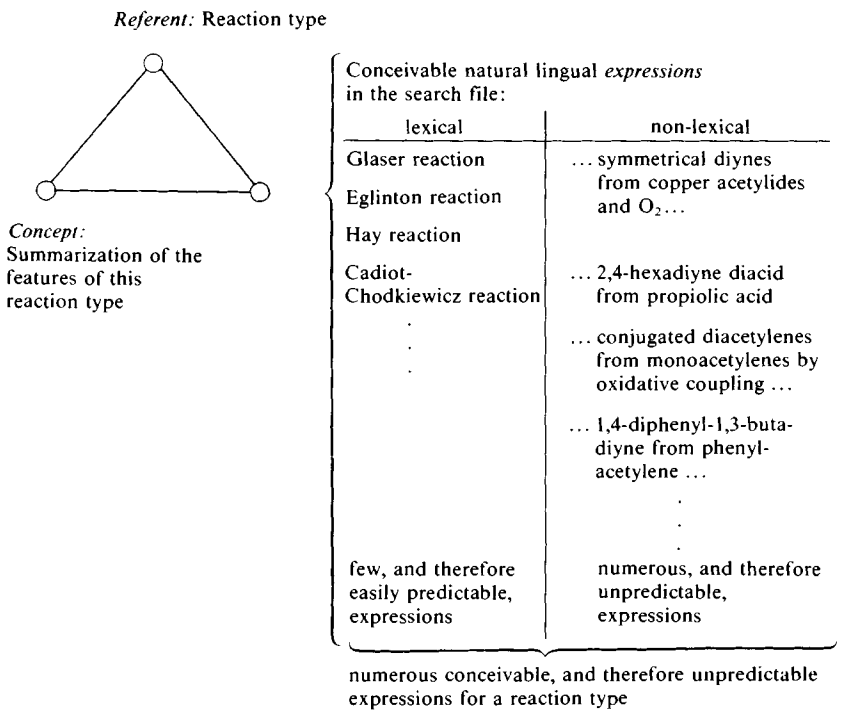


Fig. 3. Lack of predictability of unrestricted natural language expressions for a reaction type.

ever no way out, for in practice and in the case of large files one cannot possibly know through which specific examples a reaction of interest might have been represented. Knowledge about the expressions for these examples could only result from looking into the relevant texts. These are however just those still to be retrieved, and their wording cannot be anticipated. In other words, this argument requires just that to be known in advance which is still to be discovered.

3.2. Expressions for Classes of Compounds

Let us consider another example of lacking predictability of the natural, unrestricted mode of expression. A chemist may be searching a certain class of compounds. He may intend to synthesize one of its representatives, to use it as an educt, or he may be interested in the properties common to the members of this class of compounds. The corners of our semantic triangle are in this case occupied as is shown in Figure 4.

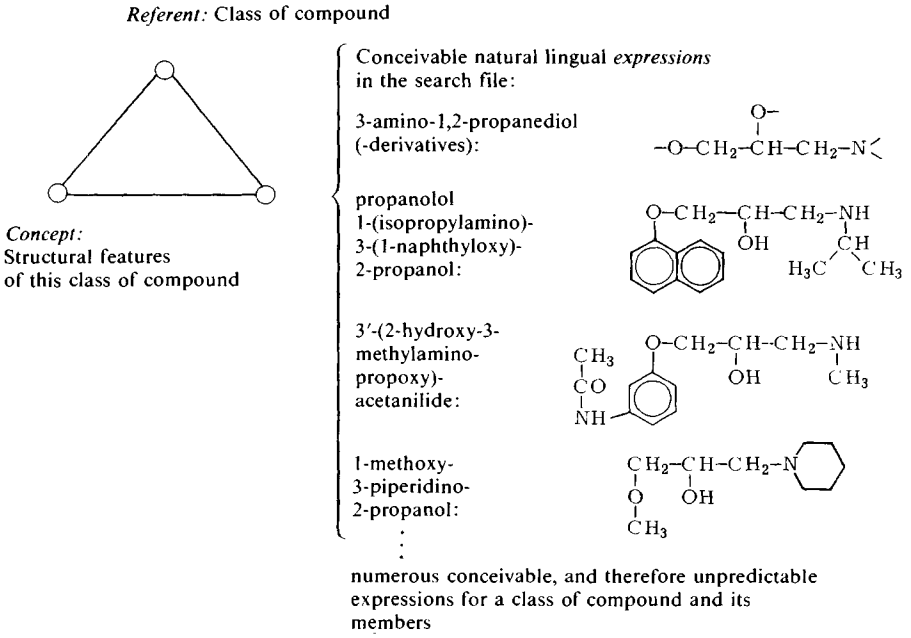


Fig. 4. Lack of predictability of unrestricted natural language expressions for a class of compounds.

Only in exceptional cases will this class of compounds be represented in the original texts through the name that the inquirer quoted, *e.g.* "3-amino-1,2-propanediol derivatives". Mostly, this class will be represented by the names of the individual compounds pertaining to this class of interest.

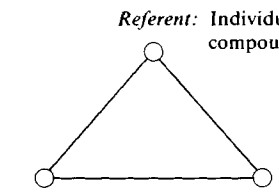
But again the number of all the conceivable individual compounds of this kind is infinitely large. Correspondingly large is therefore also the number of compound names which would have to be exhaustively enumerated as alternative search parameters in the query. An inquirer can only conjecture which of these names might in fact have entered the file. A search for a class of compounds will therefore necessarily be incomplete in a file in which compounds are represented merely by their names.

The weaknesses of search files containing unrestricted natural language texts have occasionally been attributed to the ambiguity of this mode of expression. But this cannot be the genuine reason for the seriously limited suitability of these texts for retrieval. Chemical nomenclature, for example, is extremely precise and makes possible the denotation of almost any individual molecular structure. In spite of that, it is unsuitable for the retrieval of compound classes, as we realized in the case of the aminopropanediols. Rather, the genuine source of this weakness is the impossibility of predicting at the time of commencing a search through which and how many compound names a class of chemical compounds may be represented in the search file.

It has often been argued in favor of unrestricted natural language input that it cannot lead to distortions or omissions. Although this is true it is obvious from the foregoing examples that this kind of input can lead to unsatisfactory retrieval and that a mode of expression *different* from that of the authors is indispensable.

3.3. Expressions for Individual Compounds

As another informative example, let us consider the case of individual compounds. They have always constituted an exception from the information-scientist's point of view in that they do not normally occur in the non-lexical mode of expression. One need not take into account that, *e.g.*, the individual compound in Figure 5 was represented in terms of a sentence or even several sentences. Either a name will be presented in the text or a structural formula, which however can be algorithmically transformed into a name or into a canonical connection table *i.e.*, into a variant of lexical expression (cf. [39]). Hence, only few natural-language expressions for an individual compound will be encountered, which is in sharp contrast with the expressions for reactions and compound classes. Furthermore, when compiling the names for an individual compound of interest, one need not rack one's brains for them. It is inherent in their lexical nature that they can be looked up in dictionaries, and that at these locations one will encounter additional, synonymous names or the unique Chemical Abstracts registry number. In cases of doubt any nomenclature expert will develop a name for the compound in question.—In other words, in the case of individual compounds it is well predictable through which expressions they are represented in an unrestricted natural-language file. It is correspondingly easy to phrase a query for an individual compound even for a file like this.



lexical	non-lexical
3-amino-1,2-propanediol	lacking
1,2-propanediol, 3-amino	
aminopropylene glycol	
only few expressions, which are therefore easily predictable	

Fig. 5. Good predictability of natural language expressions for an individual compound.

If in an information system one contents oneself with searching exclusively for individual compounds, then it is therefore quite adequate to accept the original, author-lingual expression for the search file. This approach suggests itself at least if the authors in the subject field are accustomed to naming their individual compounds.

4. Indexing Languages in Chemistry

We have realized in the foregoing that it is not sufficient for inquiries for reactions and classes of compounds merely to transcribe the author-lingual expressions into the search file. Rather, the essentials of any publication of potential interest must be translated into another language, and in fact into one which is more conducive to the later retrieval of these documents. We shall call this language, the task of which is to provide an enhanced representational predictability, an "indexing language" and the process of employing this language "indexing"[*].

The most obvious and natural way of representing a molecular structure is the topological method. Each atom of a structure is recorded, *e.g.* in a connection table, together with all its connections that it has in common with its neighboring atoms, and in fact at just that degree of precision which is inherent in the structural formula (cf. [36]). In contrast to the established nomenclature this representation of a substructure is independent of how it is embedded into the entire molecular structure. Hence, in the case of the aminopropylene glycols the chain of exactly three interconnected carbon atoms can be algorithmically identified in any molecule as a substructure, together with the nitrogen atom and the two oxygen atoms as substituents in exactly the correct positions.

[*] More precisely, "indexing" can be regarded as "representing the essentials of a document of potential interest with a sufficient degree of predictability and fidelity" [cf. 6, 40, 41].

The applicability of topological methods is restricted to those (sub-)structures which are defined atom by atom. The occurrence of an alkyl or alkylene residue of unspecified length and branching will defeat the topological representation of this structure. To represent general concepts like these is the domain of fragmentation codes (cf. [32-34]). In principle, fragmentation codes can represent any generalized substructure, but it is most important that they can cope with those generalizations which in fact occur in the documents of interest and in the inquiries. Purely formal generalizations will prove largely useless in practice, because they can only rarely—if at all—be employed in storage and retrieval. An example is a "fragment" for the number of rings contained in a class of molecules wanted, or the number of nitrogen and/or oxygen atoms in the members of such a class. Nor must fragmentation codes be so large and difficult to survey that they cannot be reliably employed in daily practice. This danger prevails for all those fragmentation codes which are restricted in their vocabulary and dispense with any grammar.

As far as reaction documentation is concerned, exclusively fragmentation codes are in operational use at present (*e.g.* [33-35, 37]). In principle, the reaction sites are identified and described in their state before and after the reaction. In a sequence of reaction steps several denotations pertain to one and the same reaction site (*e.g.* a carbon atom). The mutual correspondence of these denotations must also be expressed for a sufficiently precise retrieval[37].

As for the representation of non-structural concepts, it can be made sufficiently well predictable by the employment of classifications and thesauri. Chemical engineering terms and properties and uses of substances are examples of these concepts. A large variety of vocabularies is in operational use for this purpose.

5. Individual *versus* General Concept

All this raises the question to which extent our considerations on the necessity or dispensability of an indexing language can be generalized. If we could infer from a general principle, whether a concept should preferably be represented in indexing or natural language in the file, respectively, then this would be of great use.

In order to answer this question we must again undertake a short excursion into the philosophical field, and consider Figure 6.

We refer to our statement made in the foregoing that the concept is the entirety of the essential features of a referent. Through the word "essential" the marked subjectivity of concept formation is expressed and also how strongly it depends from the individual viewpoint of the human. The authoritative viewpoint in *our* considerations is that of the chemist, who, when looking at a bottle marked "aminopropylene glycol", is primarily interested in the contents of this bottle and, in fact, in the molecular structure of the contents.

Here, the primary amino group and the alcohol group will, *inter alia,* doubtlessly be considered as essential by a chemist. These two conceptual features suffice to form the meaningful general concept of the aliphatic amino alcohols. Another essential feature is the occurrence of the secondary alcohol group. If we add this feature to the general concept already discussed, we obtain the more specific

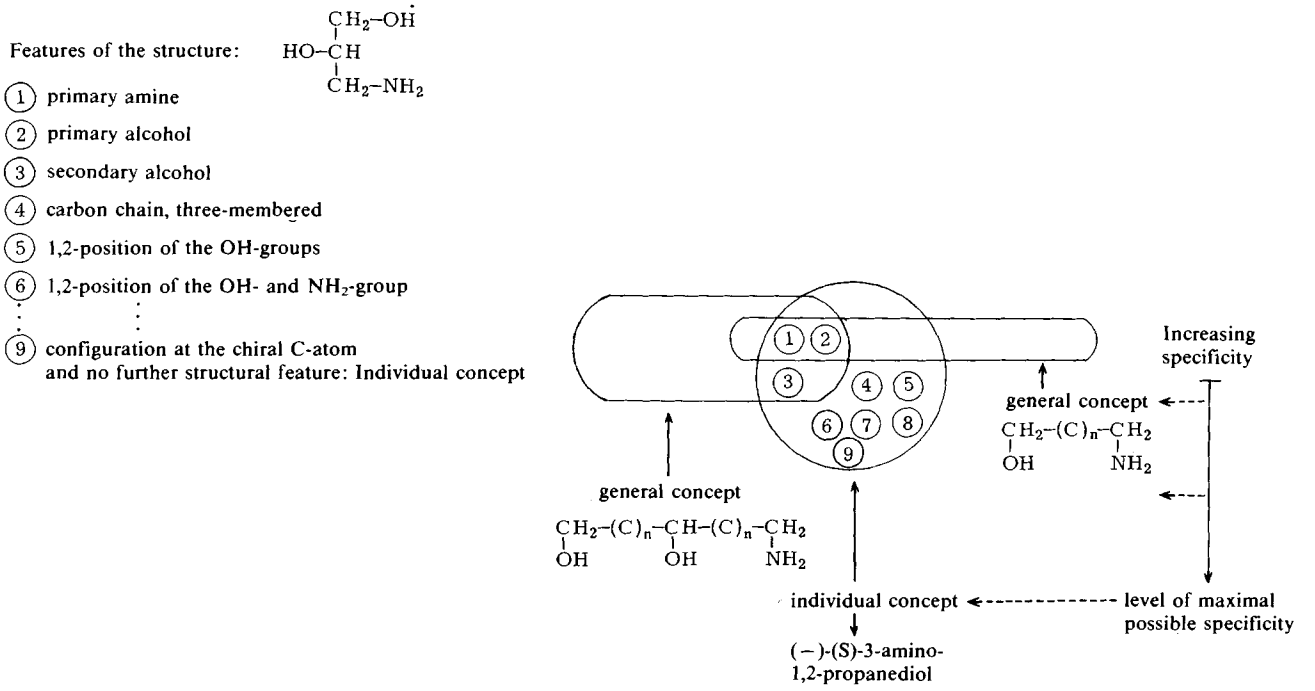


Fig. 6. Transition from general to individual concept by successive and finally complete accumulation of conceptual features.

concept of the aliphatic aminodiols. Thus, more and more features can be added to a general concept to yield more and more specific concepts. The last feature to be added may be the configuration encountered at the chiral carbon atom. Then, however, the process of making a concept more and more specific comes to an end. Admittedly, one could specify chemical, biological, and physical properties, in addition to the features already mentioned, but this would not contribute to an increased specificity of the definition of the molecule. In other words, in our process of successively making a general concept more and more specific, we have arrived at an "individual concept", *i.e.* at a concept for which no more specific concept exists which would still be meaningful to an expert of the subject field (after *von Freytag-Lörringhoff*[31]).

In what way are these considerations related with the question of indexing-lingual *vs.* author-lingual representation of concepts? Extended experience has revealed that it is markedly the general concepts for which one must take into account an almost unlimited number of (lexical or non-lexical) expressions in unrestricted natural language, *i.e.* in a mode of expression which is inherently unpredictable. Individual concepts, on the other hand, are almost exclusively expressed in the lexical manner in natural, unrestricted language, *i.e.* in a mode of expression which is fairly well predictable by nature.

If we remember an indexing language's task as one to attain representational predictability, then it is obvious that the necessity of employing an indexing language is drastically reduced in the case of *individual* concepts[5,6,13]. Seen from this angle, chemical reactions appear as *general* concepts, and it is by no means surprising that we encounter them predominantly in the non-lexical mode of expression which requires the employment of an indexing language for their improved representational predictability and retrieval. The "Glaser reaction", for example, reveals itself as a general concept in so far as it includes the—more specific—concepts of the Eglinton and Hay reactions. These reactions, too, could be subdivided further by specifying the reaction conditions, and it is immaterial whether names have hitherto been coined or not for these still more specific reactions.

Another type of generality is encountered in chemical engineering concepts, *e.g.* distillation, filtration, crystallization, *etc.* The pertinent property concepts, such as the capability of being subjected to these processes, *i.e.* of being distilled, crystallized, and many other properties and uses of matter must be counted among the general concepts as well.

A typical individual concept, on the other hand, is the author of a publication, a specific institution, a country, a patent specification, a specific book, *etc.* That all these concepts have received a proper name or a unique number, *i.e.* a lexical expression, has always considerably facilitated their handling in information systems. Thus, the indexes of authors and empirical formulas have always been faster and cheaper to compile and to search than those of general subjects.—It is true that structural formulas of individual substances and also the corresponding connection tables (cf. Section 3.3) are of the non-lexical kind, but they can easily be transformed through a machine algorithm into a canonical and, hence, lexical form, for example the one developed by *Morgan*[39]. This is due to the extraordinarily highly systematic syntax which is inherent in these connection tables, but we shall not discuss this phenomenon in more detail here.

6. The Rejection of Indexing Languages in Chemical Documentation

In many data banks, which are now accessible commercially and on-line, the employment of indexing languages has been dispensed with. The reasons given are that the high costs for reliable expert literature analyses and for sophisticated machine programs would be saved. Poor experience with certain indexing languages has also been quoted as an argument, as well as the equality or even superiority of unrestricted natural language which alledgedly could be inferred from several retrieval system evaluation experiments. Adherence to indexing languages was also said to be an obsolete attitude. These arguments have been put forward so frequently and one-sidedly that such a picture must be corrected to counteract the misdirection of development and the entering of blind alleys[42,43]. The speed and elegance of access, often over large distances, has often veiled the low retrieval accuracy, which regularly occurs when indexing is dispensed with.

As far as avoiding the expenses incurred for expert work is concerned, this is perfectly possible in the case of the individual concepts. They are easily perceived in the text and clearly delimited against other concepts through their proper names. This is in sharp contrast with general concepts. Expert knowledge is indispensable for their perception in their context, their selection, and proper designation. For example, in the literature analysis tens of thousands of individual names of peptides and fungi must be understood and identified as belonging to these general concepts. Otherwise an inquiry, *e.g.* for peptide-like bitter principles occurring in mushrooms, could not be answered, except by enumerating a very large and steadily increasing number of individual names as alternative search parameters in a query. Nobody could perform this work in advance, *i.e.* before the emergence of such a name, and include the relevant instructions in a program. It adds only to these difficulties that the meaning of words can often only be inferred from the context. This context may, however, be expressed in an unpredictable way and will thus escape any pre-programmed, mechanical analysis.

If in the renunciation of any indexing one confidently relies on future machine programs, then these would in some mysterious way have to solve a task for which the human (who would have to write these programs) does not know a solution, for, he cannot anticipate all the situations which would have to be managed by the program. How confidently would one rely on an automobile repair shop which frankly declares that only untrained people and robots are employed?

In reaction documentation the detection of the reaction site often requires expert indexers, as well as establishing the correspondence of these centers in the various educts and products. Here, the renunciation of any (mechanical

and intellectual) indexing is equivalent to the renunciation of any serviceable reaction documentation.

The possibilities and limitations of the algorithmical detection of reaction sites have been investigated by *Lynch* and *Willett et al.*[44-47]. In the REACCS system[48] of *Wipke* the algorithmical and the manual way of reaction indexing are combined.

As regards judgement of the accuracy of retrieval, it is commonly still characterized by fallacies (cf. also [38]). An inquirer who is highly satisfied with the results of a search today, may be very dissatisfied tomorrow when he realizes what and how much information has hitherto escaped him in his searches.—Often, one soothes oneself with conceding that some few "good" references are sufficient and that no search necessitates anything like a complete set of references. But is it really acceptable that the selection of these few good references is left to chance and contingency as is almost always the case in an inaccurate retrieval? In most cases an evaluation by the system user rests on a deceptive impression, for he only considers the cases of irrelevant references retrieved—because of their obviousness—and he disregards the relevant references *not* retrieved—because of their latency. A detailed investigation would reveal that any evaluative comparison of a retrieval system is surprisingly difficult, time consuming, and expensive in several respects, if conclusive results are to be attained. The literature abounds with extensive studies and everlasting controversies in this particular field.

It has also been concluded from several evaluative retrieval experiments that one could dispense with any special indexing language and that one unhesitatingly could store the texts of interest without any terminological control. But often these experiments have been conducted with unrealistically small documentation collections, in which, furthermore, one had been content with the literature over only a short period of time. Under these artificial circumstances the experimentalists have had an unnaturally good insight into the wording of the test documents, an insight which was persistently refreshed through the repetitive perusal of these documents during the experiments. Furthermore, the large heterogeneity of natural-language modes of expression, which always prevails in documentation collections that extend far into the past, cannot come into play. Under these artificial test conditions representational predictability was not seriously put to the test and largely replaced by effort of human memory. This holds particularly true when storage and retrieval have been the responsibility of one single person. Unrestricted natural language will necessarily show up deceptively well under these circumstances.

However, any translation of a text into another language encounters difficulties if the text is ambiguous and/or if in the target language there is not (yet) an appropriate expression. Translation into an indexing language does not constitute an exception to this rule. In these cases it is advisable to preserve the expressions of the original text in the search file, at least in addition to an attempted translation into indexing-lingual expressions. An indexing language vocabulary for polymer chemistry may, for example, provide only a term for the general concept of spinning. One should, however, be able additionally to enter the more specific concepts of melt spinning, dry spinning, wet spinning *etc.* into the file using these natural language terms, even if not with the degree of reliability which is inherent in the indexing language vocabulary terms. Such a combination of both kinds of language has proved extraordinarily effective in our practice and in that of the IDC[*].

7. Conclusion

In this article the question of the capabilities and limitations of natural *versus* indexing language has been raised. According to our investigations unrestricted natural language is advisable or even superior if in an information system only inquiries for individual concepts need be processed or if all the concepts of interest to an inquirer can be translated into an indexing language only with difficulties and serious distortions. An indexing language, on the other hand, cannot be dispensed with if inquiries for general concepts are also to be processed with an acceptable degree of accuracy. The reason is the inherent unpredictability of the unrestricted natural-language mode of expression for these concepts.

One should therefore refrain from generally stating that unrestricted natural language is the only reasonable choice for documentation purposes and that indexing languages are dispensable, or that precisely the contrary be valid. It should always be specified whether in the system under consideration the emphasis is on individual or on general concepts, what demands are made on the accuracy of the retrieval, and in particular, how large the document collections had been from which these conclusions have been inferred and how far these collections have extended into the past.

If high demands are made on the performance of an information system then they can be satisfied only by a well-planned combination of both kinds af language. Analysis of the problems encountered in chemical documentation suggests this conclusion most convincingly. The situation in the documentation of other fields gains much in clarity if it is seen from the same theoretical point of view. If this is kept in mind an old and highly controversial issue, on which many vehement discussions have arisen in the past, vanishes.

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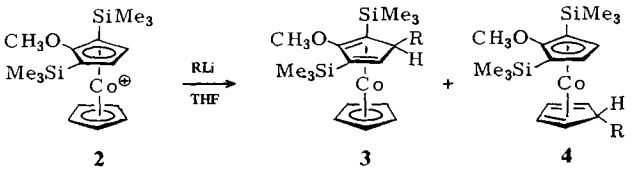
Cyclopentadienone Complexes as Synthons: Ring- and Regiospecific Nucleophilic Additions to Cobaltocenium Salts—Synthesis of Substituted Cyclopentadienes and Cyclopentenones**

By *Jeffrey P. Tane* and *K. Peter C. Vollhardt**

The recent emergence of a variety of novel cyclopentanoid natural products[1], particularly those exhibiting physiological activity, has led to a renaissance in synthetic approaches to five-membered ring compounds[2]. Few have relied on transition metal mediated or controlled CC bond formations[1,5]. We have reported on the photochemical [2+2+2] cycloaddition of two alkynes and carbon monoxide to cobalt-complexed cyclopentadienones[6] and now describe the exploitation of the metal as a stabilizing and directing group[7].



2 3 4

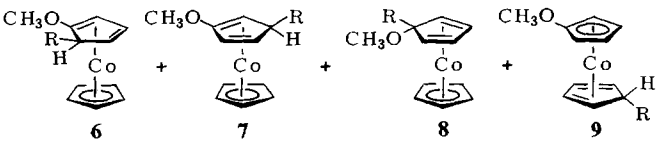
Table 2. Nucleophilic addition of RLi to **2**.

	R	3 :	4	Yield [%]
a	*t*-Bu	0	100	84
b	CH_3	29	71	98
c	*n*-C_6H_{13}—CH=CH (*trans*)	55	45	85
d	*n*-C_6H_{13}—CH=CH (*cis*)	19	81	80
e	*n*-C_6H_{13}—C≡C	73	27	95
f	Me_3Si—C≡C	80	20	83
g	CH_3O—C≡C	74	26	92
h	*t*-BuO—C≡C	69	31	94
i	C_6H_5S—C≡C	75	25	89
j	Cl—C≡C	74	26	79
k	H	75	25	100

The neutral η^4-2,5-bis(trimethylsilyl)cyclopentadienone-(η^5-cyclopentadiene)cobalt **1** gives **2** on treatment with dimethyl sulfate: **2** is converted by organolithium reagents in tetrahydrofuran (THF) into mixtures of **3** and **4** (Table 2). The observed ring selectivity is clearly suggestive of an electronic preference to attack the substituted five-membered ring, whereas steric factors force relatively bulky nucleophiles R to add to the unsubstituted ligand. The stereoretention observed in the preparation of **3c/4c** and **3d/4d** is strongly indicative of a true nucleophilic substitution mechanism.

The less substituted cobaltocenium salts **5** react with organolithium reagents to give **6**—**9** (Table 3). The results show that the additions are governed by a subtle interplay of steric, charge and orbital control; this is backed up by extended Hückel calculations.

5

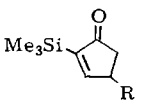


6 7 8 9

Table 3. Nucleophilic addition of RLi to **5**.

	R	6 :	7 :	8 :	9	Yield [%]
a	*t*-Bu	59	4	0	37	75
b	CH_3	64	20	0	16	82
c	*n*-C_6H_{13}—CH=CH (*trans*)	66	21	0	13	89
d	Me_3Si—C≡C	68	14	10	8	77

The synthetic utility of the method for five-membered ring compounds is demonstrated by the oxidative demetallation of **3** to furnish the free ligand, or by the application of an oxidation-hydrolysis sequence (typically $CuCl_2 \cdot 2H_2O$ or $FeCl_3 \cdot 6H_2O$ and oxalic acid) to generate potentially valuable 4-substituted 2-trimethylsilyl-2-cyclopentenones **10**—**13**.



10, R = CH_3
11, R = *n*-C_6H_{13}—CH=CH (*trans*)
12, R = *n*-C_6H_{13}—C≡C
13, R = H_3COCCH_2 (O)

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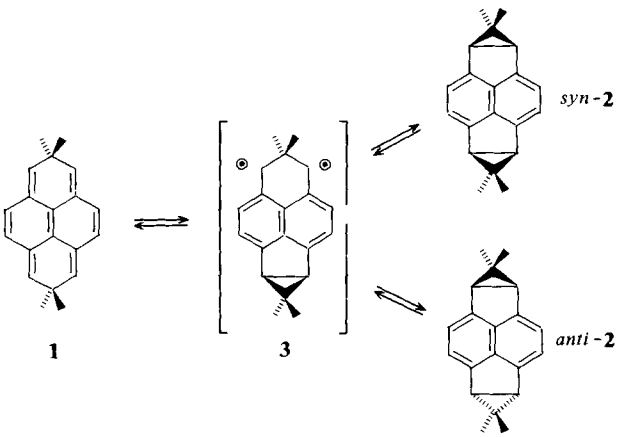
Synthesis and Valence Isomerization of 2,7-Dihydro-2,2,7,7-tetramethylpyrene**

By *Jean Ackermann, Herbert Angliker, Erich Hasler,* and *Jakob Wirz**

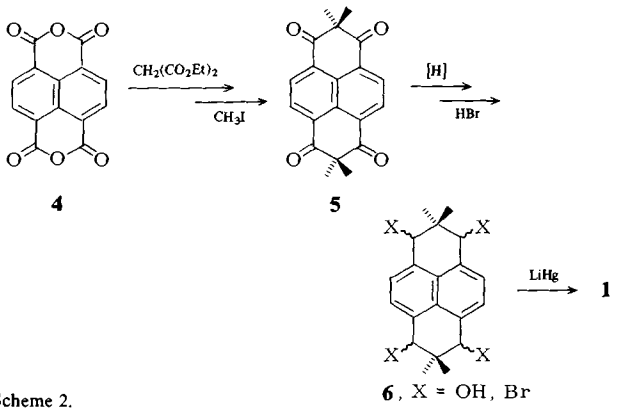
The potential to study the photochemical and thermal valence isomerization shown in Scheme 1 has been our prime incentive to synthesize the cross-conjugated polyene 2,7-dihydropyrene. We chose the blocked and sterically shielded 2,2,7,7-tetramethyl derivative **1** as a model compound to protect the system against polymerization, tautomerization, disproportionation, and oxidation. Due to geometrical constraints, ring opening of a cyclopropane fused to the *peri*-positions of naphthalene can proceed only in a disrotatory manner; the valence isomerizations **1** ⇌ *syn*-**2** and **1** ⇌ *anti*-**2** can therefore be classified as intramolecular $[_\pi 6_s + _\pi 6_s]$ and $[_\pi 6_a + _\pi 6_a]$ cycloadditions/cycloreversions, respectively. They are thus "forbidden" in the sense of the Woodward-Hoffmann rules and are likely to proceed *via* a reactive diradical intermediate **3**[3] (Scheme 1).



Scheme 1.

The preparation of **1** was achieved in a five-step synthesis starting from 1,8:4,5-naphthalenetetracarboxylic acid dianhydride **4** (Scheme 2). **1** is isolable as a yellow, crystalline solid (decomp. 180 °C) and is stable in solution in the presence of air if light is rigorously excluded. The NMR chemical shifts of the vinyl H atoms substantiate the expected polyene character of **1** and provide no evidence for the presence of an "aromatic" ring current in the central naphthalene moiety. 1,2,3,6,7,8-Hexahydro-2,2,7,7-tetramethylpyrene is obtained in quantitative yield upon hydrogenation of **1** in presence of PtO_2 in isooctane.

Solutions of **1** are rapidly bleached in diffuse daylight or upon irradiation at $\lambda = 405$ nm, whereby the valence



Scheme 2.

isomers *syn*-**2** and *anti*-**2** (≈1:1) are formed, which are readily separated by chromatography. The photoreaction is reversible upon short wavelength irradiation ($\lambda = 313$ nm), but the photostationary equilibrium is strongly temperature dependent, favoring **2** at room temperature and **1** at 77 K. The thermal equilibrium lies entirely on the side of **1** in agreement with the predictions of thermochemical additivity rules (calculated heats of formation: $\Delta_f H(\mathbf{1}) = 246$, $\Delta_f H(\mathbf{2}) = 295$ kJ/mol). However, the equilibrium between the two stereochemical isomers *syn*-**2** and *anti*-**2** proceeds at a rate which is at least two orders of magnitude faster than that of the rearrangement **2** → **1** (*ca.* 10^{-4} s^{-1} at 100 °C). We conclude that the recyclization of the diradical (**3** → **2**) requires a significantly lower activation energy than the cleavage of the second ring (**3** → **1**) although the second reaction leads to the more stable product. Clearly, the cycloreversion **2** → **1** is not a concerted process, since it requires a higher activation energy than the cleavage of only one bond to form **3**.

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CAS Registry numbers:
1, 82294-27-7; *syn*-**2**, 82294-28-8; *anti*-**2**, 82336-39-8; **4**, 81-30-1; **5**, 82294-29-9; **6** (R = Br), 82294-30-2; **6** (R = OH), 82294-31-3; **7**, 82294-32-4.

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Fourfold Bridging of the Benzene Ring in One Step[1]**

By *Brigitte Klieser* and *Fritz Vögtle**

Until now, two benzene rings could be linked by more than three bridges only *via* multistage indirect routes[2, 3, 5]. We have now found that the fourfold intermolecular coupling of *ortho*-positions can be accomplished in a single step using the "cesium effect"[8].

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[**] This work was supported by the Swiss National Science Foundation.

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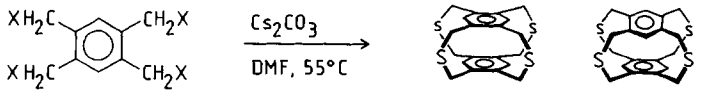
[**] This work was supported by the Fonds der Chemischen Industrie.



1 : X = SH
2 : X = Br

3a

3b

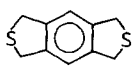
Reaction of the tetrathiol **1** with the tetrabromide **2** in dimethylformamide (DMF) in presence of Cs_2CO_3 yielded the novel tetrathia[3.3.3.3]cyclophane **3**. Previous attempts to synthesize **3** in this way—using other base-solvent combinations—resulted only in isolation of the dithia compound **4**.

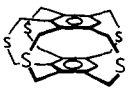
The new method led to two products (10% yield), which could be separated only with difficulty by chromatography ($R_F = 0.27$ and 0.31; TLC plates: silica gel 60 F_{254}, Merck, solvent: toluene), which we assigned as isomers **3a** and **3b** (*ca.* 1 : 1; both m.p. > 350 °C, decomp.). Their formation is expected from a consideration of molecular models. **3b** is the first (1,2,4,5)(1,5,4,2)cyclophane.

The structures of **3a** and **3b** are primarily supported by the ^{1}H-NMR spectra: Each of the isomers exhibits both a single AB system for the CH_2 protons and a singlet for the aromatic protons. This signifies that in both isomers the CH_2SCH_2 bridges are conformationally mobile, since otherwise both signals would have to be further split. Because the two benzene rings in **3b** can be mutually displaced to a lesser extent than those in **3a** due to ring strain effects, it can be assumed that the low-field shifted arene signals belong to this isomer: **3b**: $\delta_A(CH_2) = 3.75$, $\delta_B(CH_2) = 3.99$ ($J = 14$ Hz), δ(H-aromat.) = 7.73; **3a**: $\delta_A(CH_2) = 3.63$, $\delta_B(CH_2) = 4.50$ ($J = 15$ Hz), δ(H-aromat.) = 7.28.

When K_2CO_3 was used instead of Cs_2CO_3 only traces of **3** were formed. The efficacy of the carbonates corresponds to the sequence found by *Kellog et al.* in another connection[8a].

4





7

This method permits intramolecular reactions of **1** to afford five-membered rings like **4** to be suppressed in favor of dimerization; since from the first phane-sulfone pyrolysis[10] onwards sulfides have proved to be ideal intermediates for strained hydrocarbons and their oligoenes, this method signifies a considerable extension of the synthetic potential of cyclophane chemistry[3,5][***].

We were able to detect the formation of the pentathia[3.3.3.3.3]benzenophane **7**, generated using this new method, by mass spectroscopy.

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1, 82456-99-3; **2**, 15442-91-8; **3a**, 82457-00-9; **3b**, 82457-01-0; **4**, 82457-02-1; **5**, 67130-91-0; **6**, 82457-03-2; **7**, 82457-04-3.

[***] Note added in proof: in the meantime we had been able to synthesize the hydrocarbon [2.2.2.2](1,2,4,5)cyclophane on a preparative scale from the 3-sulfone.

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[10] F. Vögtle, *Angew. Chem. 81* (1969) 258; *Angew. Chem. Int. Ed. Engl. 8* (1969) 274.

H_2S as a Promotor for the Water Gas Shift Reaction**

By *Virgil I. Stenberg*, K. Raman, V. R. Srinivas, R. J. Baltisberger,* and *N. F. Woolsey*

We have found that H_2S is the first gaseous promotor of the water gas shift reaction. H_2S, a by-product from the cleaning of natural gas, crude oil or coal, is a source of hydrogen for some chemical processes; a mixture of CO and H_2S enhances coal liquefaction to an ethyl acetate-soluble material[1]. A mixture of synthesis gas and H_2S allows the best conversion of lignite into a tetrahydrofuran-soluble material[2]. Consequently, the effect of H_2S on the water gas shift reaction was examined at liquefaction temperatures (425 °C) to give a possible explanation of the liquefaction data.

Table 1. Water gas shift reaction in presence of H_2S. Reactions were performed in a 316 stainless steel batch autoclave (12 mL) using a charge of CO (48 bar, 23 mmol) and H_2O (0.42 g, 23 mmol) for 2 h at 425 °C [3].

Run No.	H_2S [mmol]	Products H_2 [mmol]	Products CO_2 [mmol]
1	0.00	0.43	0.46
2	1.66	5.64	5.27
3	2.50	6.71	5.92
4	3.33	5.23	4.95
5	4.17	5.59	5.45
6	5.01	5.83	5.54
7	0.00 [a]	0.70	4.20
8	0.00 [b]	9.50	9.72

[a] Metal sulfide layer. [b] G-3 high temperature catalyst supplied by United Catalysts Inc., Louisville, KY (USA), 10 wt.-% of CO.

The results of the H_2S-assisted shift reaction are presented in Table 1. In the absence of H_2S there is little H_2 and CO_2 formation in 2 h (run 1). However, addition of H_2S to the mixture of CO and H_2O enhances formation of H_2 and CO_2 approximately 13 fold under identical experimental conditions (cf. runs 1 and 2). No additional change in the extent of shift reaction is observed over the H_2S concentration range used (cf. runs 2–6). The reactions were carried out in stainless steel batch autoclave reactors, which became coated with a black metal sulfide layer during the reactions in presence of H_2S. This metal sulfide-coating of the stainless steel reactor is not as effective at promoting the reaction as H_2S, but is slightly better than that of the control (cf. runs 7 and 1). In run 7 there is an imbalance between the amounts of H_2 and CO_2 produced.

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This can be explained by the direct reaction of H_2 with the metal sulfide surface according to eq. (1).

$$MS + H_2 \rightarrow H_2S + M \quad (1)$$

Since CO is known to react with H_2S to give COS, which is readily hydrolyzed by H_2O [eq. (2) and (3)][4], the action of H_2S can be explained by the summation of these two equations.

$$CO + H_2S \rightarrow COS + H_2 \quad (2)$$
$$COS + H_2O \rightarrow CO_2 + H_2S \quad (3)$$

The thermal decomposition of COS into CO and S is known[5]. The slight excess of H_2 over CO_2 produced in H_2S-assisted reactions is presumably due to some decomposition of COS in competition with its hydrolysis (runs 2–6, deviation from 1 : 1 molar ratio). Run 8 shows the effect of a commercial, heterogeneous, high temperature, shift reaction catalyst on the reaction. Although H_2S is not as efficient as the solid catalyst, it holds promise by being a low cost, pumpable, recyclable gaseous catalyst.

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in shortened form on May 19, 1982 [Z 157 IE]
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CAS Registry numbers:
H_2S, 7783-06-4; CO, 630-08-0.

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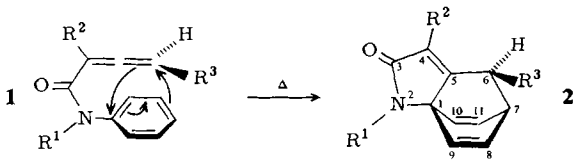
Intramolecular Diels-Alder Reaction of Allenecarboxanilides**

By *Gerhard Himbert** and *Lothar Henn*

Diels-Alder reactions have been thoroughly studied theoretically and mechanistically[1], and both the *inter*molecular[2] and *intra*molecular variants[4] are of considerable preparative importance. Here we report the first case in which a monosubstituted benzene ring assumes the diene function in an intramolecular [4+2]cycloaddition: when heated to a little over 100 °C, in the presence or not of solvent, the allenecarboxanilides **1**[11] isomerize to the tricycles **2**.



	a	b	c	d	e	f
R^1	Me	Ph	Me	Ph	Me	Me
R^2	H	H	Me	$SiMe_3$	$SiPh_3$	Me
R^3	H	H	H	H	H	$SiMe_2Ph$

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

The existence of the substituent-dependent equilibrium **1** ⇌ **2** is suggested by the fact that upon heating **2f** in xylene it is partially reconverted into the allene **1f**. Tricycles **2** could even be isolated from equilibrium mixtures, since they have higher melting points (Table 1) and crystallize more readily than the allenes **1**. We explain the astonishingly high tendency of **2** to be formed as a concurrence of several factors: The relative ease of formation of five-membered lactams, the partial activation of the benzene ring in **1** by the amino group, the increased energy-content of allenic π-systems relative to olefins, and the comparatively high rigidity in the allene and carboxamide moieties.

Table 1 (Part). Experimental and spectroscopic data of some of the tricycles **2**.

	Yield [%] [a]	t [h] [b]	M.p. [°C]	IR (KBr) [cm^{-1}] [c]	^{1}H-NMR [δ-value] [d]
a	90	9	219–221	1670 vs (branched)	3.20 (s, 3H, NMe); 5.77 (t, 4-H, ^4J=1.7); 2.30 (dd, 2H, 6-H, ^4J=1.7, ^3J=2.7); 4.09 (m, 7-H); 6.23–6.53 (m, 8-H—11-H, J_{AB}=7.1)
c	87	5	184–185	1676 sh 1670 vs 1652 s	3.21 (s, 3H, NMe); 1.75 (t, 3H, 4-Me, ^5J=1.4); 2.20 (dq, 2H, 6-H, ^5J=1.4, ^3J=2.5); 4.08 (m, 7-H); 6.21–6.51 (m, 8-H—11-H, J_{AB}=7.1)
d	47	4	124–125	1672 vs 1626 s	0.24 (s, 9H, $SiMe_3$); 2.34 (d, 2H, 6-H, ^3J=2.6); 4.15 (m, 7-H); 6.33–6.48 (m, 8-H—11-H, J_{AB}=7.1)
f	21	4.5	150–151	1672 vs	3.20 (s, 3H, NMe); 1.55 (d, 3H, 4-Me, ^5J=1.4); 0.26, 0.30 (2s; each 3H, $SiMe_2$); 2.20 (dq, 6-H, ^5J=1.4, ^3J=2.0); 3.92 (m, 7-H); 6.17–6.48 (m, 8-H—11-H, J_{AB}=7.3 and 7.6)

[a] Yields of isolated products (not optimized). [b] Reaction time (reflux in xylene). [c] Absorptions in the C=O and C=C regions. [d] Solvent: $CDCl_3$; apparatus: Bruker WP 200 (200 MHz), coupling constants in Hz.

The constitution of the isomerization products **2** is proved unequivocally by the lactam carbonyl absorptions in the IR spectra (1657—1682 cm^{-1}) and by the 4H-multiplet at δ = 6.17—6.53 (8-H—11-H), as well as the 1H-multiplet at δ = 3.78—4.15 (7-H) in the ^{1}H-NMR spectra.

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5-Pivaloyl-2*H*-isoindole—An Isolable and Crystallizable *o*-Quinonoid Heteroarene**

By *Richard Kreher**, *Norbert Kohl*, and *Götz Use*

Dedicated to Professor Georg Wittig on the occasion of his 85th birthday

Whereas 2*H*-isoindole **2a** is capable of existence in solution[1], it polymerizes in the solid state[2] at room temperature. Our results indicate that the pivaloyl group in the 5-position exerts an enormous stabilization effect: 5-pivaloyl 2*H*-isoindole **2b** is isolable in crystalline form and can be stored under nitrogen.

It can be prepared by allowing 2-mesyl-5-pivaloylisoindoline[3] to react with potassium *tert*-butylalcoholate in dimethyl sulfoxide (2 h/RT). Base-induced 1,2-elimination of methanesulfinic acid to afford 1*H*-isoindole **1b** is followed by a tautomeric rearrangement to 2*H*-isoindole **2b** (yield 94%). From the ^{1}H-NMR spectra (Table 1), the *o*-quinonoid form **2b** is present almost exclusively in organic solvents ($DCCl_3$, [D_6]dimethyl sulfoxide, [D_6]acetone), whereas even in [D_5]pyridine the benzenoid form **1b** is not detectable; the ^{13}C-NMR spectra ($DCCl_3$ and [D_5]pyridine) lead to the same result. The NH/ND exchange occurs extremely rapidly according to NMR spectroscopy; the CH/CD exchange at the 1,3-position is slower.

a, R = H; **b**, R = $(CH_3)_3C$–CO; **c**, R = $(CH_3)_3C$

Table 1. (Part) Selected physical data of **2b**.

M.p. = 115 °C; ^{1}H-NMR ($DCCl_3$/300 MHz): δ = 1.43 (s; $C(CH_3)_3$), 7.20 (ddd, J = 2.0 Hz, 0.9 Hz, 3.0 Hz; H-1), 7.35 (ddd, J = 2.0 Hz, 1.0 Hz, 3.0 Hz; H-3), 7.39 (dd, J = 9.1 Hz, 1.4 Hz; H-6), 7.57 (ddd, J = 9.1 Hz, 1.0 Hz, 1.0 Hz; H-7), 8.21 (ddd, J = 1.4 Hz, 1.0 Hz, 0.9 Hz; H-4), 9.8–10.7 (b, NH); MS (70 eV, 150 °C): *m/z* (selection) 201 (81%, M^+), 144 (100%, $M^+ - C(CH_3)_3$)

Despite its considerable kinetic stability, **2b** forms Diels-Alder adducts with *N*-alkyl- and *N*-arylmaleimides—just as does **2a**[1,2]—in solution; yields of 95% were obtained by fractionating work-up. Because of the reversible course of the cycloaddition, the *endo*-form of the 1:1 adducts is thermolabile: the *exo*-form is thermally stable. Reactions with *N,N*-dienophiles (*e.g.* dimethyl azodicarboxylate), just as those with activated alkynes (*e.g.* dimethyl acetylenedicarboxylate), proceed less readily. An umpolung of the regioselectivity of addition reactions does not occur; despite the unsymmetric substitution of the *o*-quinonoid 10π system, a substituting ene-reaction does not take place.

The enormous stabilization of the 2*H*-isoindole form **2** may be caused by the electronic interaction between the carbonyl group at the six-membered ring and the NH-group on the five-membered ring. In contrast, a *tert*-butyl group in the 5-position is not sufficient to make a 2*H*-isoindole **2c** isolable; **2c** could, however, be detected in solution by spectroscopy and *via* Diels-Alder reactions. Hence, the *tert*-butyl group in the 5-position does not have the same stabilizing effect as that in the 2-position at the heteroatom[10].

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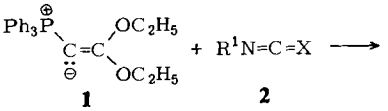
Regioselective 5-*exo-trig* Cyclization in the Reaction of [Bis(ethylthio)vinylidene]triphenylphosphorane with Heteroallenes

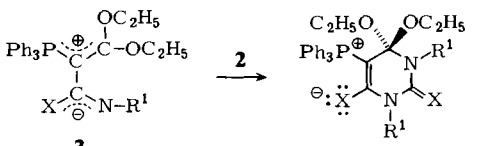
By *Hans Jürgen Bestmann** and *Kurt Roth*

Dedicated to Professor Georg Wittig on the occasion of his 85th birthday

(Diethoxyvinylidene)triphenylphosphorane **1** reacts with heteroallenes **2** (X = O, S, molar ratio 1:2) *via* intermediate **3** to give the pyrimidine derivatives **4**[1]. By analogy with **2** (**2** = **7**), [bis(ethylthio)vinylidene]triphenylphosphorane **5**[2] should form betaines **8** *via* intermediate **6**. On the basis of our earlier results[2], it was expected that in contrast to the ethoxy compounds **1**, *two* cyclization



1 **2**



3 **4**

pathways could be followed by **8**: a) 6-*endo-trig* ring-closure to **9** and b) 5-*exo-trig* ring-closure to **10**[3]. The route to **10** thus arises because the sulfur atoms are able to stabilize the negative charge on the β-C atom (relative to phosphorus)[2]. As an E1cB intermediate, **10** loses triphenylphosphane to form **11**. From studies of models, the Bürgi-Dunitz-Lehn pathway[4] for the approach of the nucleophilic N atom in **8** to the trigonal C atoms of the double bond should be considerably more energetically favorable for 5-*exo*- than for 6-*endo*-cyclization[5]. Our results confirm this. Reaction of **5** and isothiocyanates **2** (X = S) results in formation of the crystalline betaines **6**, whose

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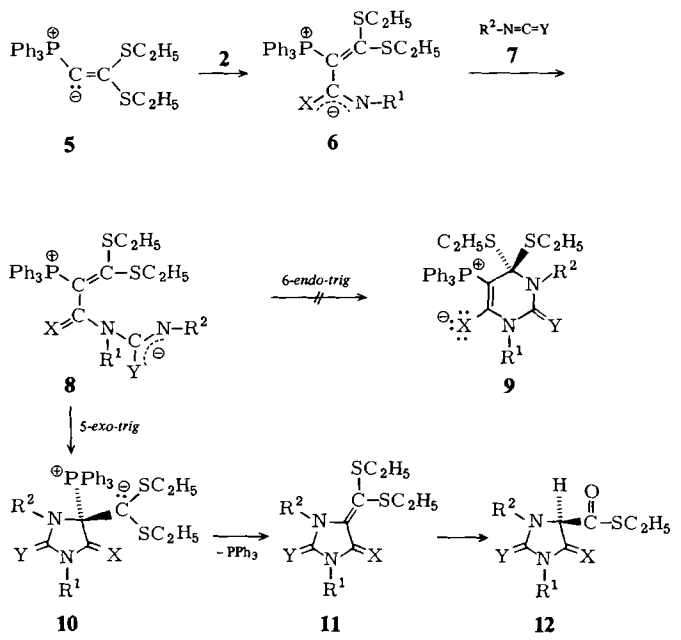
reaction with aliphatic isocyanates **7** (R^2 = alkyl; Y = O) leads regioselectively, *via* 5-*exo*-*trig* cyclization of **8** (X = S, Y = O) and subsequent displacement of triphenylphosphane, to the hydantoin derivatives **11** (X = S, Y = O). In the reaction of **5** with isocyanates **2** (X = O), the betaines **6** cannot be isolated, because they immediately react with more heteroallene **2** (**2** = **7**, X = Y = O) to afford **11** (X = Y = O) (Table 1). Pyrimidine derivatives **9** formed by 6-*endo*-*trig* cyclization could not be detected by ^{31}P-NMR or mass spectroscopy.



5 **6** **8** **9** **10** **11** **12**

Table 1. Hydantoin derivatives **11** from ylide **5** and heteroallenes **2** and **7** [a]. Correct elemental analyses and spectroscopic data were obtained for all new compounds. Yields were not optimized.

	R^1	R^2	X	Y	Yield [%]	M.p. [°C] B.p. [°C/torr] [b]
11a	CH_3	CH_3	O	O	58	39
11b	C_6H_5	C_6H_5	O	O	52	172
11c	n-C_4H_9	n-C_4H_9	O	O	51	125–130/0.05
11d	C_6H_5	CH_3	S	O	61	90
11e	CH_3	CH_3	S	O	68	115–120/0.02
11f	C_6H_5	n-C_4H_9	S	O	43	90
11g [c]	p-$CH_3C_6H_4$	CH_3	S	O	59	133

[a] **11** was synthesized under the same conditions as **4** [1]. [b] Air bath temperature in kugelrohr distillation. [c] Example of spectroscopic data: IR (KBr): 1727 (C=O) cm^{-1}. — ^{1}H-NMR ($CDCl_3$): δ = 1.28 (t, J = 7 Hz; 6H, (S—CH_2—CH_3)$_2$), 2.37 (s; 3H, —$C_6H_4CH_3$), 2.88 (q, J = 7 Hz; 2H, S—CH_2—CH_3), 3.11 (q, J = 7 Hz; 2H, S—CH_2—CH_3), 3.53 (s; 3H, N—CH_3), 7.22 (mc; 4H, aromat. H). - ^{13}C-NMR ($CDCl_3$): δ = 14.44 (s; (S—CH_2—CH_3)$_2$), 21.33 (s; —C_6H_4—CH_3), 31.34 (s; S—CH_2—CH_3), 32.16 (s; S—CH_2—CH_3), 32.70 (s; N—CH_3), 127.86 and 129.87 (each s; 4 aromat. C of the tosyl group), 131.59 (s; quaternary arom. C of the tosyl group), 134.53 and 135.87 (respectively s; C=C(SC_2H_5)$_2$), 138.94 (s; quaternary aromat. C of the tosyl group), 155.53 (s; C=O), 179.89 (s; C=S).

The thioketene derivatives **11** react with trifluoroacetic acid to afford *S*-ethyl hydantoincarboxylates **12** (**12a**: b.p. = 85–90 °C/0.02 torr).

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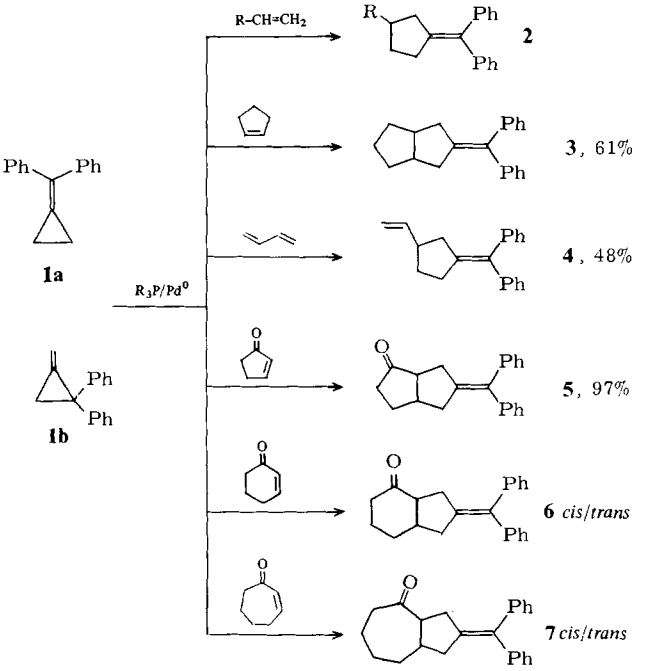
Palladium(0)-Catalyzed [3 + 2]-Cycloadditions of Diphenylmethylenecyclopropanes to Alkenes**

By *Paul Binger** and *Peter Bentz*

[3 + 2]-Cycloadditions are the simplest route to cyclopentane derivatives, which also play an important role in the synthesis of natural products. The palladium(0)-catalyzed [3 + 2]-cycloaddition of methylenecyclopropane to alkenes developed by us did not previously correspond to the requirements of a generally applicable synthesis, since it could only be carried out with a limited number of alkenes (alkyl acrylates, dialkyl fumarates or maleates, and alkenes with strained double bonds)[1]. We have now found that with 1-(diphenylmethylene)cyclopropane **1a** or 2-methylene-1,1-diphenylcyclopropane **1b** these difficulties can be overcome.

1a and **1b** react faster and more selectively than methylenecyclopropane with the above mentioned alkenes. Furthermore, 1-alkenes, cyclopentene, 1,3-butadiene, or 2-cycloalken-1-ones also undergo this Pd(0)-catalyzed reaction.



2a, R = H, 83% yield; **2b**, R = CH_3, 83%, **2c**, R = C_2H_5, 86%; **2d**, R = Ph, 88%; **6**, 76% (*cis* : *trans* = 74 : 26); **7**, 80% (*cis* : *trans* = 16 : 84); the values given are crude yields for the reaction with **1a** (determined by GC). All compounds were characterized by elemental analysis and spectroscopic methods.—Example: **2c**, synthesized from **1a**, iPr$_3$P, (η^5-C_5H_5)(η^3-C_3H_5)Pd (25 : 1 : 1) in toluene, 0 °C, 1.5 bar, 1-butene.

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[**] This work contains parts of the dissertation planned to be presented by P. Bentz, Universität Kaiserslautern in 1982.

Irrespective of the substitution pattern of educt **1** (**1a** or **1b**), 3- or 3,4-substituted, 1-(diphenylmethylene)cyclopentanes are obtained, mainly in high yields, after 1–8 h at 80–130 °C.

1-(Dialkylmethylene)cyclopropanes are less suitable as educts, since their isomerization to 1,3- and/or 1,4-alkadiene derivatives, which is also catalyzed by Pd(0), on the whole proceeds faster than the desired cycloadditions.

The methylenecyclopentane derivatives **2**–**7** are, in part, interesting educts for the synthesis of natural products containing cyclopentane, since **2**–**7** can be converted readily *via* ozonolysis into cyclopentanone derivatives and, *e.g.*, instead of pure 1-alkenes, heteroatom-containing 1-alkenes, 1,x-dienes, or enynes, whose middle double or triple bonds do not react in these [3+2]cycloadditions, can also be used.

In **1** the reactivity of the double bond is markedly less than in methylenecyclopropane. Consequently, Pd(0)-catalyzed cyclodimerization of **1** largely does not occur, and hence cycloadditions to less reactive olefins also become possible. The formation of the same final products **2**–**7** irrespective of whether **1a** or **1b** is used requires an isomerization during the reaction. This should occur in an organopalladium intermediate that can be written in several valence isomeric forms[1,3,4].

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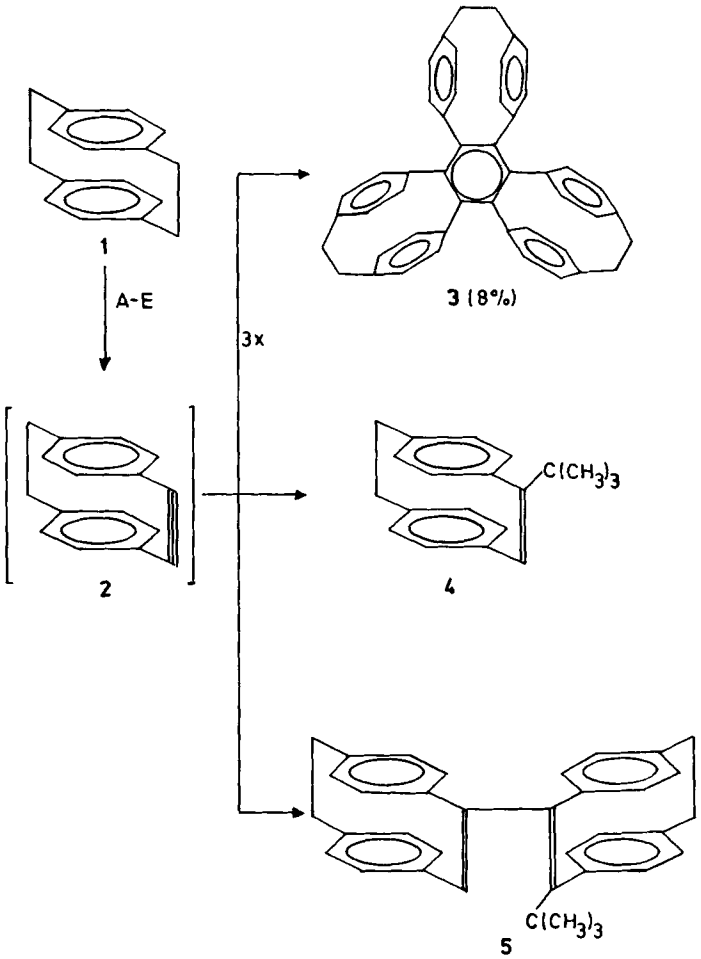
Trifoliaphane—The Trimer of a [2.2]Paracyclophane with an Ethyno-Bridge**

By *Manfred Psiorz* and *Henning Hopf**

The tendency of strained cycloalkynes to participate in addition reactions has been especially valuable for the synthesis of polycyclic hydrocarbons[1]. We were interested whether the 1-alkyne **2** may be generated from [2.2]paracyclophane **1**, and whether the former, presumably very reactive "cyclophyne" trimerizes to the hexaphenylbenzene derivative **3**. In contrast to hexaphenylbenzene itself, which in its crystalline state possesses a propeller-type structure with a pitch of 65°[2], in **3** the benzene rings, because of the bridging, should be aligned in a parallel fashion and perpendicular to the central ring; this structural feature could give rise to an electronic interaction between the peripheral rings extending like a torus around the inner, orthogonal π-system.



Scheme 1. A: anhydrous CCl_4, 2000 W-daylight lamp, Br_2; B: KO*t*Bu, dimethyl sulfoxide, 1 h, 20 °C (A and B 44% yield); C: toluene, PCl_5, 1 h, reflux (63%); D: *t*BuOH, 1 M KO*t*Bu, 1 h, reflux (95%); E (lithiation/elimination): a) *t*BuLi, 2 h at −60 °C in tetrahydrofuran (THF); b) add solution in boiling THF dropwise, 2 h reflux.

Hydrocarbon **3** (dec. >360 °C) may indeed be obtained from **1** by the five-step reaction sequence shown in Scheme 1. The proof of structure for **3** rests on the mass spectrum [(*m/z* 612 ($M^{\oplus}$, 61%), 306 ($M^{2\oplus}$, 100%) and predominantly on the NMR-spectra [^{1}H-NMR ($CDCl_3$, int. TMS): $\delta = 3.02$ (s, 12H, ethano-bridges), 6.65 (q, pseudo-AB-system $J_{AB} = 4.5$ Hz, 24H, aromatic protons); ^{13}C-NMR ($CDCl_3$, int. TMS): $\delta = 141.15$ (s), 140.04 (s), 138.87 (s), 133.03 (d), 132.49 (d) and 34.93 (t)]. The vibrational spectrum [(KBr): $\nu = 3000$ (m), 2920 (s), 2845 (m), 1587 (s-m), 1490 (m), 1392 (m), 1088 (m), 925 (m), 760 (m), and 719 cm^{-1} (vs)] and electronic spectrum [(CH_3CN): $\lambda_{max} = 307$ ($\varepsilon = 1400$), 230 (51000), 210 nm (3900)] are comparatively simple and unstructured, respectively, and resemble the corresponding spectra of **1** and [2](4,4'')orthoterphenylophane[3]. The last elimination step provides, besides **3**, varying amounts of the etheno-bridged paracyclophanes **4** and **5**[4], supporting the intermediate formation of **2**, since analogous alkylation and coupling products arise from other strained cycloalkynes as well[5].

We suggest the trivial name trifoliaphane for the novel hydrocarbon **3**, since its structure reminds one of a three-

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[**] Cyclophanes, Part 17. For Part 16 see: R. Allmann, M. Nagel, S. El-tamomy, H. Hopf, *Chem. Ber.*, in press.

leaved clover when viewing the molecule along the C_3-axis.

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1, 1633-22-3; **2**, 82444-97-1; **3**, 82444-98-2; **4**, 82444-99-3; **5**, 82445-00-9

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Ferromagnetic Interaction between Orthogonal "Magnetic" Orbitals in Dinuclear $Cu^{II}Cr^{III}$ Complexes

By *Yves Journaux, Olivier Kahn**, and *Hubert Coudanne*

One of the goals of our work on heterodinuclear complexes is to design a synthetic strategy to compounds exhibiting intramolecular ferromagnetic coupling. We have previously obtained the $CuVO(fsa)_2en \cdot CH_3OH$[1] and $CoCu(fsa)_2en \cdot 3H_2O$[2] complexes [$(fsa)_2en^{4-}$ is a bichelate ligand derived from the Schiff base 3,3'-ethylenebis(nitrilomethylidyne)disalicylic acid]. In both cases, the "magnetic" orbitals[3]—singly occupied orbitals of transition metal ions, which are partly delocalized in the direction of the surrounding ligands—of both metal ions are strictly orthogonal. We now describe a heterodinuclear complex in which one of the two metal ions possesses more than one unpaired electron.

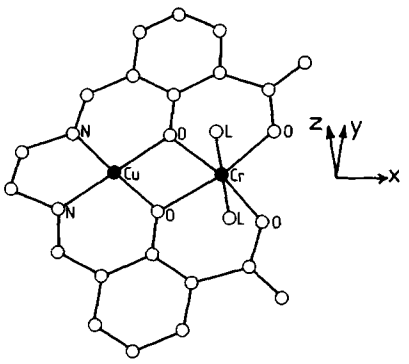


Fig. 1. Schematic representation of the structure of $[Cu^{II}Cr^{III}(fsa)_2enL_2]^+$.

$[Cu^{II}Cr^{III}(fsa)_2en(H_2O)_2]Cl \cdot 3H_2O$ **1**, the first $Cu^{II}Cr^{III}$ complex, also has strictly orthogonal magnetic orbitals. Indeed, if the Cu^{II} ion is in a planar N_2O_2 environment and the Cr^{III} ion in a pseudo-octahedra $O_2O_2L_2$ environment (see Fig. 1), the symmetry of each metallic site is very close to C_{2v}. It turns out that the unpaired electron on the Cu^{II} occupies a xy-type orbital (B_1) and that the three unpaired electrons around Cr^{III} occupy x^2-y^2, xz, and yz-type orbitals (A_1, B_2, and A_2, respectively). There is no overlap between the B_1 magnetic orbital around Cu^{II} and the A_1, B_2, and A_2 magnetic orbitals around Cr^{III}, and this makes pairing of electrons in MO's of low energy unfavorable. Consequently, it might be predicted that the $Cu^{II}Cr^{III}$ complex would exhibit strong ferromagnetic interaction.

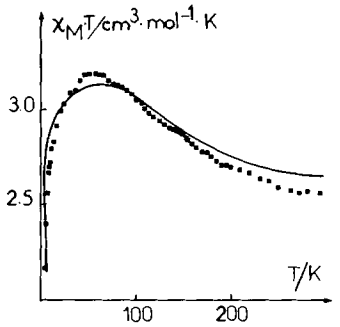
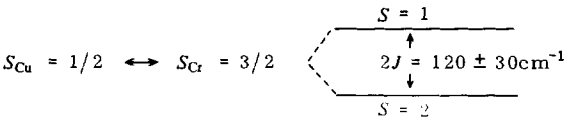


Fig. 2. Temperature dependence of $\chi_M T$ for **1**. ■: experimental points; — calculated curve.

Figure 2 shows the temperature dependence of the product of the molar magnetic susceptibility χ_M temperature T between 4 and 300 K. $\chi_M T$ increases as **1** is cooled from 300 K to about 45 K, reaches a maximum (3.19 cm^3 mol^{-1} K), and then decreases below this temperature. Qualitatively, the interpretation of the curve is straightforward. The interaction between the Cu^{II} doublet and the Cr^{III} quartet states gives rise to two spin states characterized by $S=1$ and $S=2$, the latter being the lower in energy. The maximum value of $\chi_M T$ corresponds to what it is expected for a totally populated quintet ground state without first order angular momentum. The decrease of $\chi_M T$ below 45 K could be due to the combined effect of intermolecular interaction and zero field splitting of the ground state quintet. Quantitatively, an agreement between calculated[4] and observed $\chi_M T$ values is obtained for a triplet-quintet energy gap $2J$ between triplet and quintet states of 120 ± 30 cm^{-1} (Scheme 1).



Scheme 1.

The intramolecular ferromagnetic coupling observed in this $Cu^{II}Cr^{III}$ pair confirms the concept of orthogonality of the magnetic orbitals.

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[4] *Procedure:* **1**: A suspension of $CrCl_3 \cdot 6H_2O$ (124.8 mg, 0.47 mmol) and $[CuH_2(fsa)_2en \cdot 0.5H_2O]$ [5] (200 mg, 0.47 mmol) in 150 mL of CH_3OH is refluxed. After about three weeks, a limpid dark blue solution is obtained. Well formed blue single crystals, which were characterized by elemental analysis, result from slow evaporation.

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Functionalization at Proanomeric Centres by Photobromination: A Novel Access to Oxo- and Acyloxyimino-glycosyl Bromides**

By *Frieder W. Lichtenthaler** and *Pan Jarglis*

Dedicated to Professor Hermann Schildknecht on the occasion of his 60th birthday

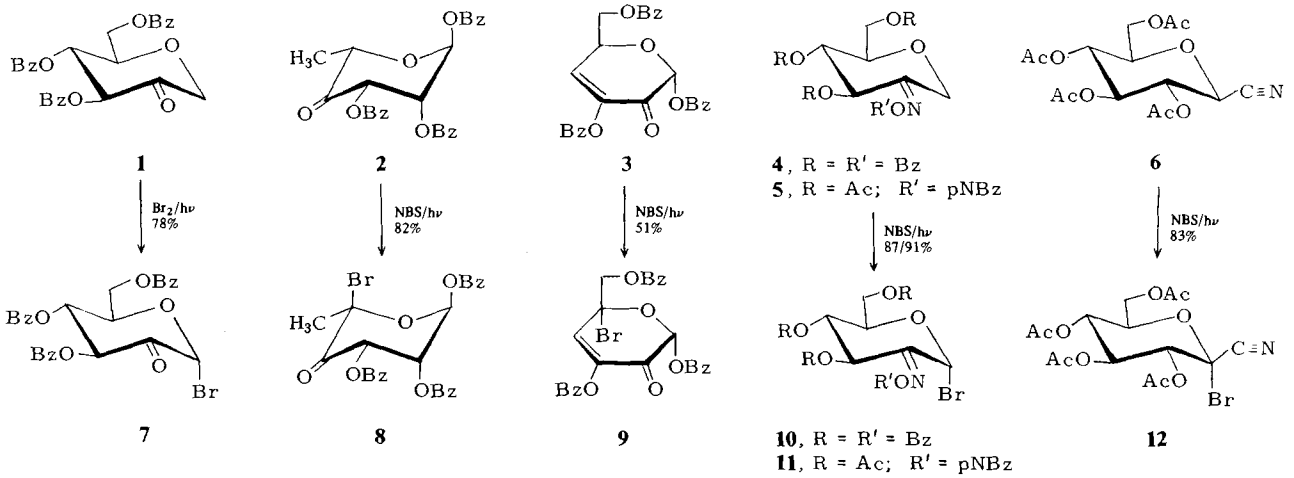
The range of reactions undergone by sugars at the anomeric centre form the backbone of carbohydrate chemistry[2]. In contrast, reactions of monosaccharides at their proanomeric centres, *i.e.* those which become anomeric by introduction of a functional group at C-4 in furanoid or at C-5 in pyranoid systems, are rare; they usually involve elaboration of a double bond in the proanomeric position and subsequent addition reactions[3] or free-radical bromination[4] which, however, mostly give low to moderate yields.

By placing an electron acceptor group, *i.e.* oxo- or acyloxyimino functionalities next to the proanomeric centre, its C—H bond becomes push-pull—or capto-datively[7]—substituted, and, hence, highly radicophilic. Thus, radical reactions proceed with considerably greater ease with higher regio- and stereoselectivity, as is amply demonstrated by the smooth, high yield photobrominations of **1**—**6** (cf. Scheme 1).

With **1** and **2**, photobromination is essentially stereospecific, and no products other than α-glycosyl bromides **7** and **8** are obtained which have high potential for the preparation of α- and β-linked glycosyl glycosides. Enolones are also readily accessible, since alcoholysis under slightly basic conditions is accompanied by β-elimination. Accordingly, upon *in situ* anomerization with tetraethylammonium bromide followed by methanolysis **7** preferentially affords (isolated yield: 66%) the α-D-enolone (**3**, OMe instead of α-OBz), whereas exposure to methanol in the presence of $NaHCO_3$ yields the respective β-D-anomer (80%).

In the tribenzoyl enolone **3** the proanomeric centre is vinylogously push-pull activated, yet due to the presence of only one conformationally determining substituent in the radical intermediate, a 3:1 mixture of anomers result, of which the major, α,α-isomer **9**, is isolable in 51% yield.

Utilization of hydroxyimino functions as the captive ("pull") element of a capto-dative system also requires protection of this OH group, which is most suitably effected by benzoylation. Thus, the peracylated 1,5-anhydro-D-fructose derivatives **4** and **5** readily give the oximinoglycosyl α-bromides **10** and **11** in high yield. The availability of such α-bromides in stable, storable form is capable of providing an efficient access to amino sugar-containing oligosaccharides by simple displacement of the bromine *via* a Königs-Knorr glycosylation reaction, reduction, and deblocking. This approach has close analogies to *Lemieux*'s nitroso-halogenide procedure[21], yet holds the additional advantage that disaccharide-derived analogs of **10** and **11**, which constitute versatile building blocks for the construction of lactosamine-, maltosamine-, and cellobiosamine-containing oligosaccharides, may easily be prepared. The



Scheme 1. Photobrominations in refluxing CCl_4 by irradiation with a 250 W tungsten lamp or a 450 W IR heat lamp, 15—60 min.—Abbreviations: Ac = acetyl; Bz = benzoyl; pNBz = *p*-nitrobenzoyl; NBS = *N*-bromosuccinimide.—New educts: **2** (m.p. = 190—192 °C, $[\alpha]_D^{20}$ −10° in $CHCl_3$, 94%) by pyridinium chlorochromate oxidation of 1,2,3-tri-*O*-benzoyl-α-L-rhamnose; **4** (m.p. = 138—139 °C, $[\alpha]_D^{21}$ −37° in $CHCl_3$, 91%) and **5** (89—90 °C, −70°, 85%) by acylation of the free oximes [20] with benzoyl chloride and p-nitrobenzoyl chloride/pyridine, resp.—Products: **7** (m.p. = 174 °C, $[\alpha]_D^{21}$ +185° in $CHCl_3$), **8** (118—119 °C, +109°), **9** (181—183 °C, −21 °C), **10** (138—139 °C, −37 °C), **11** (amorph., +156 °C), **12** (92 °C, +137 °C).—For ^{1}H-NMR data and experimental procedures for **7**, **10**, and **12** see Supplement.

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[**] Sugar Enolones, Part 16. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 15: P. Jarglis, F. W. Lichtenthaler, *Angew. Chem. 94* (1982) 140; *Angew. Chem. Int. Ed. Engl. 21* (1982) 141; *Angew. Chem. Suppl. 1982*, 175.

nitrile **6** can also be readily photobrominated at the push-pull substituted proanomeric centre.

Attempts to prepare the chloride analog of **7** by photobromination of **1** with *N*-chlorosuccinimide under a variety of conditions failed. However, refluxing **1** and **4** in CCl_4 with sulfonyl chloride/azobisisobutyronitrile (3—4 h, 76 °C) leads cleanly to the respective, highly stable α-

glycosyl chlorides **7** (Cl instead of Br, m.p. = 153–154 °C, $[\alpha]_D^{20}$ +155° in $CHCl_3$, 87%) and **10** (Cl instead of Br, syrup, $[\alpha]_D^{22}$ +198° in $CHCl_3$, 90%).

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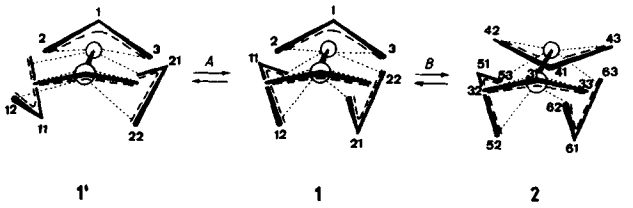
Two-Dimensional Dynamic ^{13}C-NMR Spectroscopy—An Investigation of $(\eta^3\text{-}C_3H_5)_4Cr_2$

By *Reinhard Benn**

Chemical exchange processes were hitherto investigated NMR spectroscopically almost solely by line-shape analysis[1] and magnetization-transfer methods[2]. It has already been shown[3] that exchange networks can be obtained directly with the aid of two-dimensional NMR spectroscopy (2D-NMR). In the following it is demonstrated with tetraallyldichromium $(\eta^3\text{-}C_3H_5)_4Cr_2$ as example, that two-dimensional ^{13}C-^{13}C-shift correlation diagrams are especially suitable for the qualitative investigation of exchange processes.



In [D$_6$]benzene at 30 °C $(\eta^3\text{-}C_3H_5)_4Cr_2$ is present as a 60:40 mixture of the isomers **1** and **2**. Each isomer has two *trans* η^3-allyl groups bridging the metal atoms. The other two η^3-allyl ligands are *cis*-oriented in **1** and *trans*-oriented in **2**[4]. Accordingly, the noise-decoupled ^{13}C-NMR spectrum of **1** shows seven signals, that of **2** twelve signals (Table 1); these were assigned on the basis of a two-dimensional ^{13}C-^{1}H-shift correlation diagram[5] using the ^{1}H chemical shifts[4].

The structural dynamic behavior of **1** and **2** can be deduced from the two-dimensional ^{13}C-^{13}C-shift correlation diagram without a detailed knowledge of the assignment. A section from the contour plot of the ^{13}C-^{13}C-shift correlation diagram is shown in Figure 1. The positions of the ^{13}C-NMR signals are given as contour lines on the middle line; for clarification the conventional one-dimensional ^{13}C-NMR spectrum is reproduced at the top of Figure 1. In the two-dimensional spectrum further contour lines, so-called cross peaks, appear above and below the middle line. Differences in the ^{13}C chemical shifts are indicated on the vertical axis; related cross peaks have the coordinates $[\delta_a; \frac{1}{2}(\delta_a-\delta_b)]$ and $[\delta_b; \frac{1}{2}(\delta_b-\delta_a)]$[3]; *e.g.* the cross peaks of C21 and C11 connected by an extrapolated line have the coordinates (106.90; 2.35) and (102.20; −2.35). These cross peaks provide direct evidence of an exchange of C21 with C11, which is caused by a 180° rotation of the

Table 1. ^{13}C-NMR data (δ values) of **1** and **2**; solvent: C_6D_6; temperature: 30 °C; concentration *ca.* 15%.

1		**2**	
C-atom	δ value	C-atom	δ value
1	130.20	31	130.58
2	70.99	32	72.79
3	76.58	33	75.80
11	102.20	41	135.24
12	58.91	42	69.68
21	106.90	43	76.23
22	56.39	51	102.88
		52	57.94
		53	54.64
		61	104.96
		62	55.27
		63	54.01

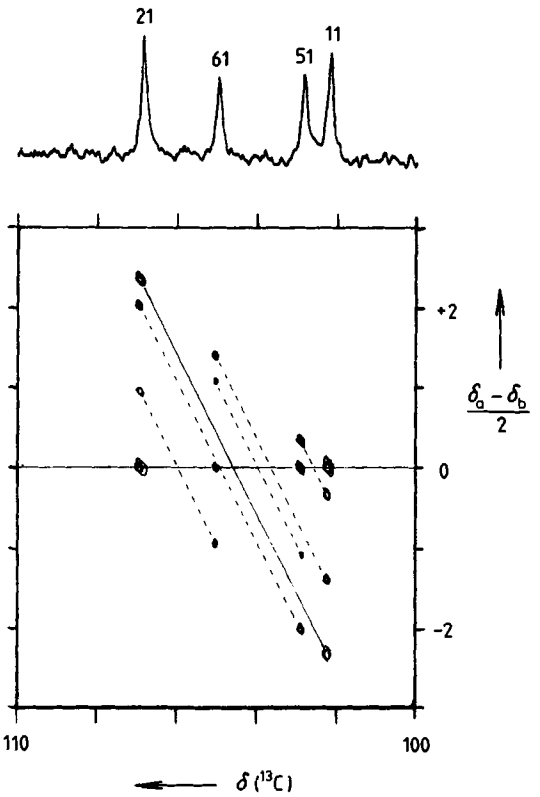


Fig. 1. Top: Conventional one-dimensional ^{13}C-NMR spectrum (100.61 MHz).—Bottom: Section from the two-dimensional ^{13}C-^{13}C shift correlation diagram of $(\eta^3\text{-}C_3H_5)_4Cr_2$ in [D$_6$]benzene (δ = 128.5); recorded with a 90°-(t_1/2)-90°-Δ-90°-(t_1/2)-FID(t_2) pulse sequence [3]. t_1 was varied from 0 to 0.0256 s over 256 points, the mixing time Δ was 2 s. The ^{13}C-NMR signals are represented on the horizontal axis, and shift differences on the vertical axis. Exchanging ^{13}C-atoms appear as cross peaks and are connected together.

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bridging η^3-allyl groups (in phase with respect to the NMR time scale) (Process *A*; **1** and **1'** are mirror images). In addition, two further cross peaks each are observed on the vertical axis of the signals of C21 and C11: the peaks belonging to them, with which they are connected by dotted lines, lie on the vertical axis of δ(C61) and δ(C51). These cross peaks indicate a second exchange process (*B*), namely the exchange of **1** with **2**, most likely by rotation of a non-bridging η^3-allyl group about the metal-metal axis. As a result of both processes C21 is exchanged with C61 and C51, and C11 with C61 and C51, respectively; a further consequence is the exchange of C51 with C61. The relevant cross peaks are likewise connected by a dotted line.

^{13}C-^{13}C-exchange networks, in contrast to those of protons, have the advantage that cross peaks do not occur as a result of homonuclear scalar couplings or nuclear-Overhauser interactions[3]. It would therefore appear that a ^{13}C-^{13}C-shift correlation diagram is the best method for the qualitative investigation of exchange processes in the case of readily soluble samples.

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$(\eta^3\text{-}C_3H_5)_4Cr_2$, 12295-17-9.

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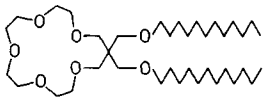
Double Layer Formation with a Surfactant-Type Crown Ether Complex: Crystal Structure of 15,15-Bis(dodecyloxymethyl)[16]crown-5 · NaSCN**

By *Mátyás Czugler, Edwin Weber*, Alajos Kálmán, Birgitta Stensland,* and *László Párkányi*

Crown ethers containing structural units which are typical for surfactants[1a] are of interest for problems of energy transport and storage and in organic semiconductor and liquid-crystal technology[1b]. We report here for the first time on the molecular structure of a surfactant-type crown ether alkali metal ion complex and on the state of order in the crystal lattice.



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The crown ether **1**[2] forms a 1:1 complex with NaSCN in acetone/ether (yield 75%, colorless platelets, m.p. 75–77 °C). According to an X-ray structure analysis of this amphiphilic complex (Fig. 1) the conditions within the crown ether moiety closely resemble those in the Na^+-complex of the unsubstituted [15]crown-5[4].

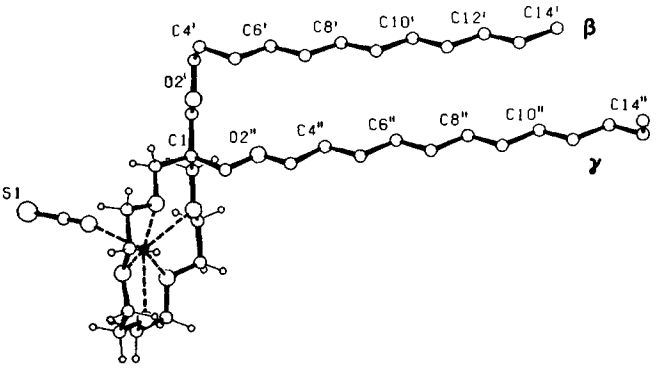

Fig. 1. Structure of **1** · NaSCN in the crystal (average distances: NaO = 243 pm, NaN = 233.4 pm).

Surprisingly, the tail groups differ from each other considerably in their conformation: The chain pseudoaxial to the crown ether ring plane ("γ-chain") is, with exception of the C13"C14" bond (*gauche* arrangement), *all-trans* configurated, whereas in the pseudoequatorial chain ("β-chain") a characteristic *helical kink* arises from the presence of two immediately consecutive *gauche* arrangements at the C4' atom.

Thus, the structure of the crystalline **1** · NaSCN complex shows interesting parallels to membrane-forming lipids such as 3-lauroylpropanediol-1-phosphorylcholine monohydrate (LPPC)[6] or egg phosphatidylcholine (EPC)[7]: the expanse of the crown ether head group (70 $Å^2$) closely approaches that found at the surface of EPC vesicles (74 $Å^2$[7]); crystalline LPPC shows an analogous helical kink, which lies merely one C-atom nearer to the chain terminal[6].

The *double layer structure* of type "M//"[6] characteristic for LPPC crystals is also found in the crystals of **1** · NaSCN, the head and tail groups of the ligand each being aggregated (Fig. 2). Interlamellar contacts protruding out from the "anionic" sides of the crown ether rings (external surface of the double layer) do not exist. In the crystal of **1** · NaSCN the double layer has a diameter of 2270 pm, in LPPC crystals it is only slightly thicker (2350 pm)[6].

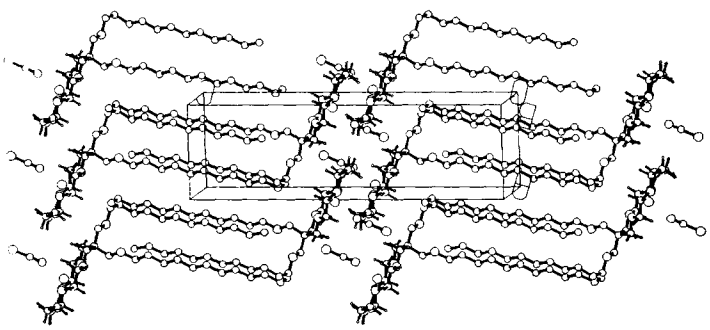

Fig. 2. Molecular packing in the crystal of the **1** · NaSCN complex showing the unit cell (as in Fig. 1, the H-atoms have been omitted for clarity).

These results demonstrate that such surfactant crown ethers and their complexes are suitable as model compounds for biogenic lipid molecules; this is important in as much as the fine structure of natural membrane-forming compounds could so far be determined only in very few cases and with limited accuracy. It is suggested that the free ligand **1** could be used as an ion-selective membrane carrier.

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1, 79992-69-1; **1**·NaSCN, 82445-02-1

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cis-$[Ru(bpy)_2(CO)H]^+$ — A Possible Intermediate in the Photochemical Production of H_2 from Water Catalyzed by $[Ru(bpy)_3]^{2+}$?**

By *John M. Kelly** and *Johannes G. Vos*

The intensity of interest in the chemistry of bipyridyl complexes of ruthenium has been largely generated by the use of these complexes as intermediaries in the photodissociation of water by visible light[1]. Another possible approach would be to use hydride complexes as the hydrogen-evolving centers with the same complex possibly also acting as primary electron acceptor. We now report the ready preparation of the PF_6 salt of $[Ru(bpy)_2(CO)H]^+$, a complex cation which in aqueous solution below pH 7 is converted into $[Ru(bpy)_2(CO)(H_2O)]^{2+}$ and H_2.

cis-$[Ru(bpy)_2(CO)Cl]^+$ and $NaBH_4$ react in aqueous ethanol to give *cis*-$[Ru(bpy)_2(CO)H]^+$ **1**, the complex being isolated as its hexafluorophosphate derivative in greater than 70% yield. The corresponding 4,4′-dimethylbipyridyl derivative *cis*-$[Ru(C_{12}H_{12}N_2)_2(CO)H]^+$ **2** was prepared analogously. Both products gave satisfactory elemental analysis and were identified by IR and NMR spectroscopy. A singlet in the ^{1}H-NMR of **1** at $\delta = -11.47$ is direct evidence for the presence of the hydride ligand[2], whereas the resonances in the region $\delta = 7.2-9.3$ are those expected for the 16 magnetically nonequivalent bpy protons (the two different *cis*-bpy ligands have different environments). The carbonyl stretch ν_{CO} for **1** at 1930 cm^{-1} is at a lower wavenumber than that in $[Ru(bpy)_2CO(Cl)]^+$ and other $[Ru^{II}(bpy)_2(CO)X]^{n+}$ complexes[3], consistent with the electron donating ability of the hydride ion. The absorption spectrum of the PF_6 salt of **1** (over the range 300 nm to 600 nm) is given in Figure 1 together with those of $[Ru(bpy)_2(CO)Cl]^+$ **3** and $[Ru(bpy)_2(CO)_2]^{2+}$ **4**. In **3** or **4** the metal-ligand charge transfer (MLCT) band, which is found in the visible region in many other $Ru(bpy)_2$ complexes[3], is shifted to shorter wavelengths. The spectrum of **1** is distinguished by a band at 448 nm, which may possibly be due to an MLCT transition. It is probable that the lowest excited state of **1** is different from that of **3** and **4**, since irradiation of methanolic solutions of **1** ($\lambda > 330$ nm) leads only to very slow decomposition, whereas decarbonylation of other $[Ru^{II}(bpy)_2(CO)X]^{n+}$ complexes takes place rapidly under identical irradiation conditions.

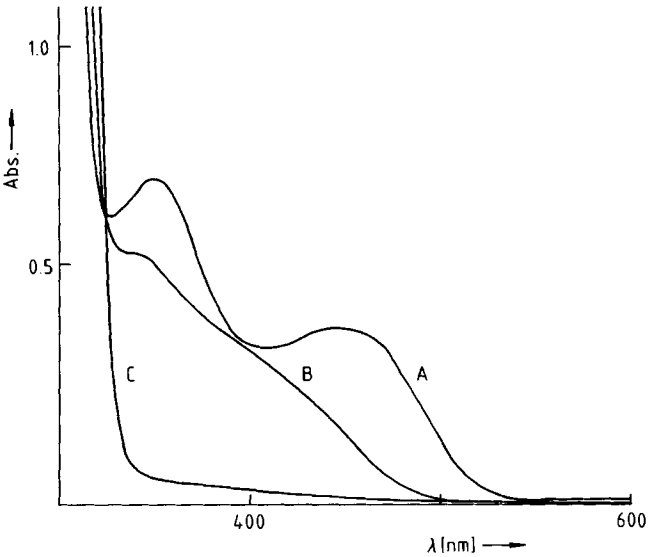

Fig. 1. Absorption spectra of 1.0×10^{-4} M CH_3CN solutions of the PF_6 salts of $[Ru(bpy)_2(CO)H]^+$ **1** (A), $[Ru(bpy)_2COCl]^+$ **3** (B), and $[Ru(bpy)_2(CO)_2]^+$ (C).

The hydride complex cations **1** and **2** are stable in organic solvents or in weakly alkaline aqueous buffer solution (*e.g.* at pH 9.1). In the presence of acid, however, **1** decomposes rapidly giving $[Ru(bpy)_2(CO)(H_2O)]^{2+}$ **5** and H_2 [eq. (a)]. The aquocomplex **5** was identified from its NMR and UV/VIS spectra by comparison with an independently prepared sample[5a], and the H_2 detected by mass spectrometry[5b]. The decomposition of **1** proceeds slowly even in neutral aqueous solutions and more rapidly in weakly acidic solution. At pH 5.1 (0.1 M potassium hydrogen phthalate buffer) the half-life of **1** at 18 ± 1 °C is *ca.* 10 min.

$$\underset{\mathbf{1}}{[Ru(bpy)_2(CO)(H)]^+} + H_3O^+ \rightarrow \underset{\mathbf{5}}{[Ru(bpy)_2(CO)H_2O]^{2+}} + H_2 \quad (a)$$

The observation that this relatively photostable hydride complex may be readily prepared and that it rapidly decomposes in weakly acid solution to give H_2 suggests that it may well be able to act as a hydrogen producing center in photocatalytic reactions. It is interesting to note that **1** is prepared from $[Ru(bpy)_2(CO)Cl]^+$, which we previously[3] showed to be a substantial byproduct of the reaction used to prepare $[Ru(bpy)_2Cl_2]$ for the synthesis of surfactant derivatives of $[Ru(bpy)_3]^{2+}$[6a]. Although monolayers of these surfactant derivatives were initially reported to sensitize photoproduction of H_2 from water, this was not the case for carefully purified samples, and it was assumed that some unidentified impurity was responsible for the observed activity[6a,b]. It is intriguing to speculate whether hydride complexes such as **1** might have played a role in the original photoreaction. Complexes such as **1** and **2** may also have potential as water gas shift or hydroformylation catalysts, particularly in view of the recent report that $[Ru(bpy)_2COCl]^+$ acts as a catalyst for the photo-induced water gas shift reaction[6c].

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Procedure

$[Ru(bpy)_2(CO)Cl]ClO_4$ (0.5 g) in refluxing ethanol/water (2 : 1 v/v) was treated with $NaBH_4$ (0.5 g) dissolved in the minimum of water. After being refluxed for 20 min, excess of an aqueous solution of NH_4PF_6 was added. Upon standing (12 h) crystals formed in the solution (yield 0.42 g; 80%). The crude material was further purified by chromatography on neutral alumina using acetone as eluent, and then recrystallized from acetone/water mixtures. The orange crystals obtained were dried *in vacuo* at room temperature. $1 \cdot PF_6 \cdot 0.5(CH_3)_2CO$: ^{1}H-NMR (80 MHz, CD_3CN); $\delta = 9.1-9.3$ (m, 2H), 7.2—8.6 (m, 14H), 2.09 (s, 3H), −11.47 (s, 1H). UV/VIS (CH_3CN) $\lambda_{max} = 275$ ($\lg\varepsilon = 4.48$), 353 (3.70), 448 (3.49). IR (KBr): $\nu_{CO} = 1930$ cm^{-1}.

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CAS Registry numbers:
1 · PF_6^-, 82414-89-9; **2**, 82414-90-2; **3** · ClO_4^-, 76549-23-0; **4**, 75550-96-8; $[Ru(bpy)_3]^{2+}$, 15158-62-0.

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[6] a) G. Sprintschnik, G. W. Sprintschnik, P. P. Kirsch, D. G. Whitten, *J. Am. Chem. Soc. 98* (1976) 2337; *99* (1977) 4947; b) S. J. Valenty, G. L. Gaines, *J. Am. Chem. Soc. 99* (1977) 1285; A. Harriman, *J. Chem. Soc. Chem. Commun. 1977*, 777; c) D. J. Cole-Hamilton, *ibid. 1980*, 1213.

Designed Synthesis of an Alkylidyne-Capped Trinuclear (Mo, Mo, W) Metal Cluster**

By *F. Albert Cotton** and *Willi Schwotzer*

Methods for the intentional assembly of preselected metal atom clusters (designed syntheses) are still scarce. This is particularly true for the so-called "electron-poor trinuclear clusters" recently reviewed[1] and currently under active study here and elsewhere[2, 3]. We report here on a successful designed synthesis that has led to a mixed-metal cluster compound with the metal atoms (namely Mo and W) in relatively high oxidation states (average = 10/3) and a capping alkylidyne ($\equiv C-C_6H_5$) group. The new compound **1** has been conclusively identified (NMR, IR) and structurally characterized by X-ray crystallography. Not only is the cluster compound of interest, but the reaction used to prepare it is a paradigm for other such syntheses.

The preparative method used was the following:

$$(\eta^5\text{-Cp})(OC)_2Mo{\equiv}Mo(CO)_2(\eta^5\text{-Cp}) + \textit{trans}\text{-}Br(OC)_5W{\equiv}CC_6H_5 \rightarrow$$

$$Mo_2WBr_3(CO)_3(\eta^5\text{-Cp})_2(CC_6H_5)$$

1

The principle involved[4] is the addition of an M≡M bond to an M′≡CR bond to generate a tetrahedral cluster of the type $M_2M'C$[5]. There are some additional complications involved in this particular reaction since the Br/W ratio in the product (3 : 1) is greater than that in the reactant (1 : 1) and some CO is eliminated. These features of the reaction are still under study.

The product **1**, after chromatographic purification, is obtained as a brownish-black crystalline solid (yield 20%) that slowly decomposes in moist air. The crystal contains molecules (Fig. 1) in which an isosceles triangle of two Mo atoms and one W atom, bonded to each other, is capped by a C_6H_5C group that forms a C—M bond to each metal atom. On the opposite side of the Mo_2W plane there is a bridging CO group across the Mo—Mo bond and bridging Br atoms across each Mo—W bond. Three ligands (Br, 2CO) complete a distorted octahedron around the W atom, and the η^5-C_5H_5 ligand on each Mo atom can be considered, formally, to occupy three mutually *cis* octahedral coordination sites on those atoms. The structure is thus of the same type already well known[1] for $[Mo_3O_4F_9]^{5-}$, $[W_3O_4F_9]^{5-}$, and many complexes of the trinuclear aquomolybdenum(IV) ion.

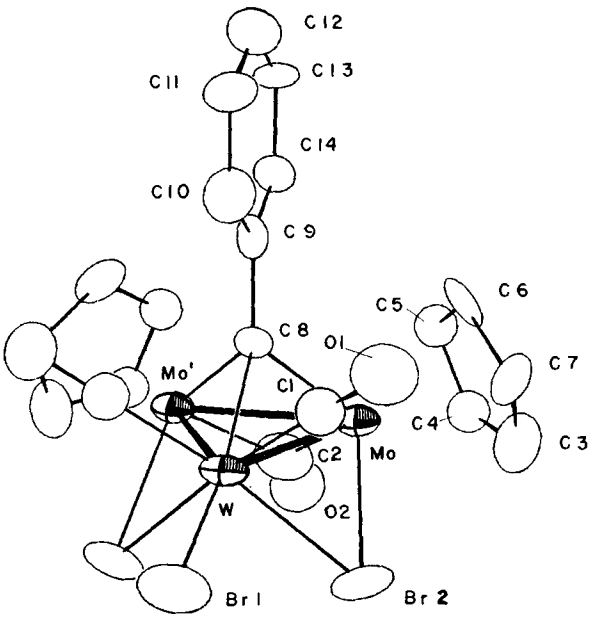

Fig. 1. ORTEP drawing of the molecular structure of **1**. The metal atom cluster, Mo_2W, and the metal-metal bonds are shown with heavier lines at the center.

Some important bond lengths [pm] are: Mo—Mo, 276.6(3); Mo—W, 264.7(2); Mo—CPh, 198(1); W—CPh, 215(2). Compound **1** crystallizes in the space group Pnma with $Z = 4$; each molecule has a crystallographic plane of symmetry containing the W, μ-CO, the entire capping group, and the terminal Br atom. Assigning valences of −1 to the Br and C_5H_5 groups, −3 to PhC and −2 to μ-CO, the Mo_2W cluster is found to have 8 electrons. According to previous analyses of bonding in cluster compounds with this type of structure[3] this gives rise to a set of three single bonds with two additional electrons occupying a delocalized, symmetrical molecular orbital that is slightly antibonding with respect to the Mo_2W ring.

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[**] This work was supported by the National Science Foundation.

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[4] Reaction of the reactants in the molar ratio 1:1, tetrahydrofuran (THF), 12 h, room temperature, chromatography on silica gel (toluene/THF).
[5] Similar reactions have been investigated by F.G.A. Stone et al. (F. G. A. Stone, private communication).

Coupling of Sterically Hindered Peptide Bonds—A Renaissance of the Acid Chloride Method**

By *Hans-Heinrich Bechtolsheimer* and *Horst Kunz**

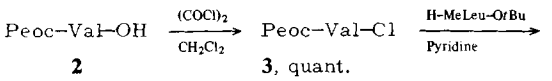
Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

Because of the high incidence of side reactions, high susceptibility to racemization, and contamination by phosphorus compounds, activation of the carboxy group *via* the acid chloride has largely lost significance in peptide synthesis[1]. The advantages of the high reactivity of the acid chloride are thus no longer exploited.

However, in the coupling of sterically demanding amide bonds, as they frequently occur *e.g.* in natural depsipeptides, a strong activation of the carboxylic acid cannot be circumvented. Hence, for the formation of the strongly hindred amide bonds of sporidesmolic acid B **1** *Ovchinnokov et al.*[2] resorted to the acid chlorides of *N*-and *O*-benzyloxycarbonyl-protected synthons, despite the danger of benzyl chloride cleavage and the side reactions of the Leuchs-anhydrides.

H-Hyiv-Val-MeLeu-OH **1**

The extremely acid-stable 2-(triphenylphosphonio)-ethoxycarbonyl (Peoc) protecting group developed by us[3] now enables synthesis of the stable acid chlorides of the amino and hydroxy acids, even at room temperature. In contrast to amino acids with other N-protecting groups even oxalyl chloride can be used as reagent. For example, after addition of reagent at 0 °C in dichloromethane, the acid chloride **3** is smoothly generated from Peoc-valine **2**



2 **3**, quant.

Peoc–Val–MeLeu–O*t*Bu

4, 81%

on warming to room temperature. Since only volatile by-products are formed there is no fear of contamination of the resulting peptides. Solvent and excess oxalyl chloride are removed *in vacuo*. Because of its high reactivity we could couple **3** with *N*-methylleucine *tert*-butyl ester to give the Peoc-dipeptide ester **4**, for the synthesis of **1**. This process, which requires 1 h at −20 °C, followed by 12 h at room temperature, is of general utility for the synthesis of sterically hindered peptide bonds.

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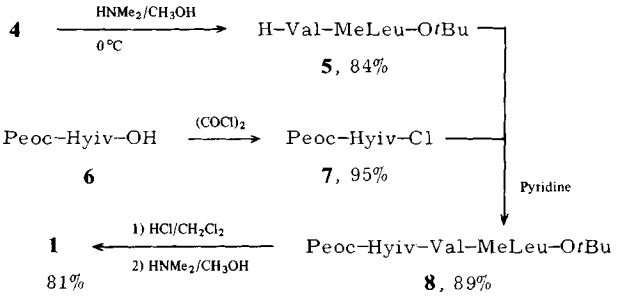
After removal[3] of the Peoc group from **4**, **5** is coupled with the free amino function on the *O*-Peoc-hydroxyisovaleroyl chloride **7** obtained from **6**[4] to give the completely protected sporidesmolic acid B derivative **8**. The structure of **8** was confirmed by the 200-MHz ^{1}H-NMR spectrum.—



Successive cleavage of the *tert*-butyl group and the Peoc group at 0 °C affords the free sporidesmolic acid B **1**. Its melting point and IR spectrum were identical with those of an authentic sample obtained from natural sporidesmolide I[5]. The rotation ($[\alpha]_D^{21} = -106.7$ ($c = 0.47$, glacial acetic acid)) also almost reached that of the natural product ($[\alpha]_D^{19} = -108$, glacial acetic acid), thus indicating that no racemization has taken place on using this acid chloride method despite the twofold activation and condensation involved.

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CAS Registry numbers:
1, 3200-76-8; **2**, 61083-76-9; **3**, 82414-77-5; **4**, 82414-76-4; **5**, 82414-78-6; **6**, 82414-79-7; **7**, 82414-80-0; **8**, 82414-81-1; H-MeLeu-O*t*-Bu, 42807-86-3.

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New Method for the Synthesis of *N*-Vinylamides**

By *Günter Schmitt** and *Wolfgang Ebertz*

Dedicated to Professor Friedrich Asinger on the occasion of his 75th birthday

Attempted basic hydrolysis of 2-ferrocenyl-2-oxazolines, interesting intermediates for the preparation of 1,2-disubstituted ferrocenes[2], led to the discovery of novel, general reaction patterns for 2-oxazolines. It was found that 2-oxazolines **1** having at least one H-atom in the 4-position always isomerize to *N*-vinylamides **2** on reaction with potassium *tert*-butoxide (KO*t*Bu) in solvents such as hexamethylphosphoric triamide (HMPT), dimethyl sulfoxide or dimethoxyethane if C-5 is substituted by at least one alkyl

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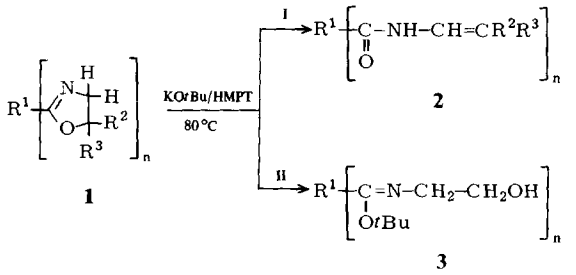
or aryl group (Route I). If the 5-position bears only hydrogen atoms then *tert*-butyl *N*-(2-hydroxyethyl)imidates **3** are formed (Route II). The reactions always proceed selectively in only one direction, irrespective of the type of substituents at the 2-position. Table 1 lists some examples.

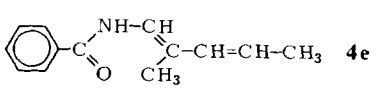
Table 1. Reaction of 2-oxazolines **1** in the system KO*t*Bu/HMPT [a]. n = 1; in the case of **1i**, n = 2. Ferr = ferrocenyl.



Cpd.	R^1	R^2	R^3	*t* [h]	Product	Yield [%] [b]
1a	CH_3	H	CH_3	16	**2a** [d]	[c]
1b	CH_3	CH_3	CH_3	18	**2b**	[c]
1c	$(CH_3)_3C$	H	CH_3	18	**2c** [d]	25
1d	$(CH_3)_3C$	CH_3	CH_3	18	**2d**	30
1e	C_6H_5	H	CH_3	1.3 [e]	**2e** [d]	76
1f	C_6H_5	H	C_6H_5	1.5 [f]	**2f** [d]	70
1g	C_6H_5	CH_3	CH_3	18	**2g**	86
1h	*o*-$H_2NC_6H_4$	H	CH_3	17	**2h** [d]	67
1i	*p*-C_6H_4	H	CH_3	7 [e]	**2i** [d]	90
1j	Ferr.	H	CH_3	16	**2j** [d]	70
1k	Ferr.	CH_3	CH_3	4	**2k**	83
1l	CH_3	H	H	18	**3a**	[c]
1m	$(CH_3)_3C$	H	H	18	**3b**	34
1n	C_6H_5	H	H	18	**3c**	50
1o	Ferr.	H	H	196	**3d**	28

[a] Molar ratio KO*t*Bu : **1** = 5 : 1; 80 °C. [b] The isolated products gave correct elemental analyses and spectroscopic data. [c] Not isolated; same boiling point as HMPT, soluble in water. Characterization by ^{1}H-NMR in HMPT. [d] Mixture of the *Z*- and *E*-form; *Z*-fraction 70–75%. [e] 110 °C. [f] 100 °C.

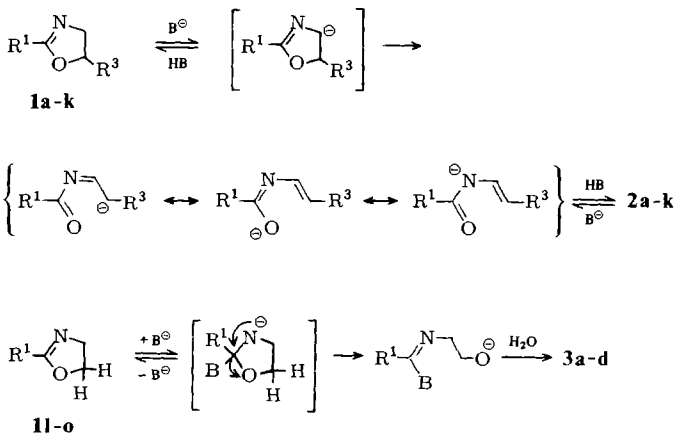
The rate of reaction strongly depends on the temperature and on the molar ratio KO*t*Bu : **1**. Thus, *e.g.*, reaction of **1e** in the system KO*t*Bu/HMPT at 100 °C with a molar ratio KO*t*Bu : **1e** of 5 : 1 proceeds quantitatively only after about 2 h, at 140 °C even after 2 min. A molar ratio of KO*t*Bu : **1** = 5 : 1 is recommended for syntheses on a preparative scale. A sudden drop in the rate of reaction is observed at molar ratios of less than 2 : 1. At a molar ratio of 1.5 : 1 quantitative conversion requires 5 h. With equimolar amounts of KO*t*Bu and **1** the reaction is even slower, and the vinylamide **2** formed as intermediate reacts further to give a byproduct; *e.g.* **1e** reacts at 110 °C to give **4e** (22% yield).



4e

According to current interpretations of the reaction mechanism the products **2** and **3** are formed as shown (B = *t*Bu).

This novel method can be exploited for the preparation of variously substituted *N*-vinylamides in satisfactory to good yields from 2-oxazolines, which in turn are readily accessible *via* numerous routes[4]. Because of its broad spectrum of use this new method is, from a preparative



point of view, far superior than any of the previously reported methods.

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1a, 6159-22-4; **1b**, 4195-89-5; **1c**, 82495-87-2; **1d**, 82495-88-3; **1e**, 23437-02-7; **1f**, 22020-69-5; **1g**, 33561-48-7; **1h**, 82495-89-4; **1i**, 53720-68-6; **1j**, 82511-69-1; **1k**, 82511-70-4; **1l**, 1120-64-5; **1m**, 30393-80-7; **1n**, 7127-19-7; **1o**, 82511-68-0; (*E*)-**2a**, 5202-80-2; (*Z*)-**2a**, 5202-79-9; **2b**, 5202-82-4; (*E*)-**2c**, 69775-44-6; (*Z*)-**2c**, 69775-43-5; **2d**, 82495-90-7; (*E*)-**2e**, 5202-76-6; (*Z*)-**2e**, 5500-46-9; (*E*)-**2f**, 78007-47-3; (*Z*)-**2f**, 5202-77-7; **2g**, 5202-81-3; (*E*)-**2h**, 82495-91-8; (*Z*)-**2h**, 82495-92-9; (*E, E*)-**2i**, 82495-93-0; (*Z, Z*)-**2i**, 82495-94-1; (*E, Z*)-**2i**, 82495-95-2; (*E*)-**2j**, 82511-65-7; (*Z*)-**2j**, 82511-66-8; **2k**, 82511-67-9; **3a**, 82495-96-3; **3b**, 82495-97-4; **3c**, 82495-98-5; **3d**, 82511-64-6; **4e**, 82495-99-6

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[4] J. A. Frump, *Chem. Rev. 71* (1971) 483.

Controlled Modification of Crystal Habit by "Tailor-Made" Impurities: Application to Benzamide**

By *Ziva Berkovitch-Yellin, Lia Addadi, Marian Idelson, Mein Lahav,* and *Leslie Leiserowitz*

Minute amounts of impurities (or additives) present in solution during crystallization may have a pronounced effect on the crystallization process, in particular on the morphology of the deposited crystals[2]. We previously reported changes in habit of amino acids and derivatives induced during crystallization by the presence of minute amounts of chiral impurities of similar structure to the substrate[4–7]. Through these changes a stereochemical correla-

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tion was established between the molecular structure of the impurity, the crystal structure of the substrate, and the effected growth directions, leading to a proposal of a two-step mechanism for the binding of the impurity at the growing crystal faces and retardation of growth. We have found that slightly modified substrate molecules yield impurities which are particularly effective in inducing such morphological changes.

By application of these principles it becomes possible to grow crystals with desired morphologies by "tailoring" impurities which bind at a preselected face and thus inhibit growth in a predictable manner. An advantage of this method is that the effect of factors such as temperature, solvent, and supersaturation may be kept constant by performing all crystallization experiments under identical conditions, except for the nature and concentration of the impurity. This approach is illustrated here for benzamide.

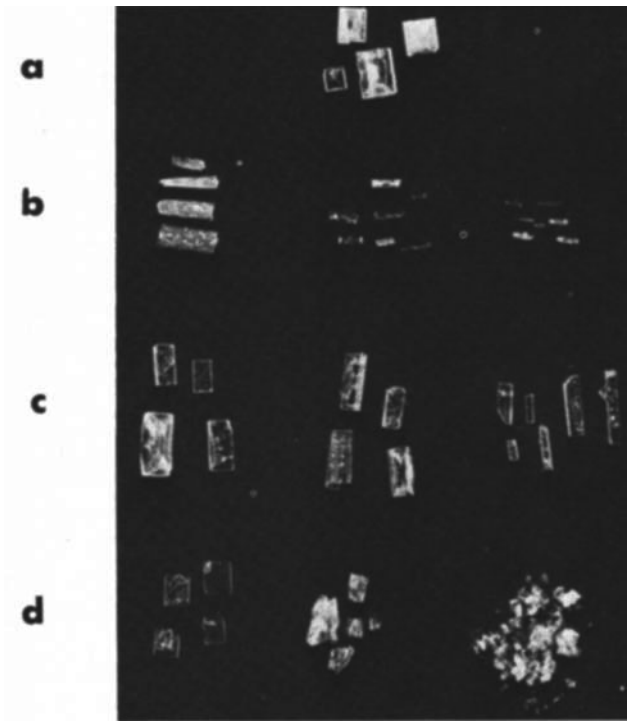

Fig. 1. Crystals of benzamide grown in absence and in presence of increasing amounts of impurities: a) pure benzamide, b) with benzoic acid (3%, 5%, 10%), c) with *o*-toluamide (1%, 5%, 10%), d) with *p*-toluamide (3%, 5%, 10%).

Benzamide crystallizes from ethanol in plate-like crystals elongated along the *b*-direction (Fig. 1a). The general features of this morphology may be rationalized in terms of the packing characteristics.

In the light of the correlation between the crystal structure and morphology of benzamide, it was possible to choose impurities to specifically modify the relative rates of growth along the three principal directions: Retardation of growth primarily along the *b*-axis was achieved by adding benzoic acid. This induces the crystals to grow in rod-form extending along the *a*-direction (Fig. 1b). Retardation of growth along the *a* axis was achieved by adding 1—10% of *o*-toluamide to the mother solution. This induces the crystals to grow in the form of rods extending along the *b*-direction (Fig. 1c). Finally, as expected, thinner and thinner platelets (Fig. 1d) were obtained by adding increasing amounts of *p*-toluamide.

In all cases the habit was modified gradually with the concentration of impurity in solution (Fig. 1). HPLC analysis indicates that only 0.2—0.5% impurities are found in the bulk of the crystal, even when the amount in solution was as high as 10%.

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CAS Registry number:
Benzamide, 55-21-0.

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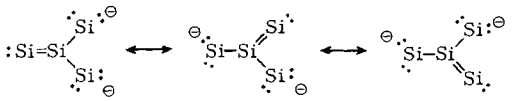
$Li_{12}Si_7$: Theoretical Interest Aroused

By *Joel F. Liebman** and *James S. Vincent**

Von Schnering et al. recently reported[1] the remarkable crystal structure of $Li_{12}Si_7$, a compound containing planar Si_4 star clusters and planar Si_5 rings. For our description of these two inherent structures we present here alternatives and precedents based on qualitative and quantitative MO considerations or on comparisons with isoelectronic species.

We start with the Si_4 stars, which contain singly coordinated terminal silicon atoms, as found in HNSi and H_2CSi[3]; they can be formulated as Si_4^{-2} (**A**).

This anion is "π-isoelectronic" with the Y-aromatic[6] carbonate ion CO_3^{2-}, *i.e.* both ions have the same number of π-electrons and atoms. Because of the smaller charge, Si_4^{2-} should be more stable than the Si_4^{8-} species postulated by *von Schnering et al.*[1].



A

Also, because of the high charge, the existence of the postulated Si_5^{8-} and Si_5^{10-} anions[1] is not very likely. In our opinion the Si_5 rings should be formulated as Si_5^{6-} ions; such species are π-isoelectronic with the well-known cyclopentadienide ion. The possible presence of the 2π Si_5^{-2} species has also been considered. From symmetry considerations and mathematical operations, as well as consideration of the crystal structure, we deduced that lithium is present as Li^+ and Li_3^+ in $Li_{12}Si_7$[10]. We therefore suggest that $Li_{12}Si_7$ be formulated as $Li_{24}Si_{14} \equiv (Li^+)_9(Li_3^+)_5(Si_4^{2-})(Si_5^{6-})_2$.

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CAS Registry number:
$Li_{12}Si_7$, 76036-33-4.

[1] H. G. von Schnering, R. Nesper, J. Curda, K. F. Tebbe, *Angew. Chem. 92* (1980) 1070; *Angew. Chem. Int. Ed. Engl. 19* (1980) 1033.
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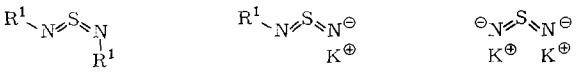
Dipotassium Sulfur Diimide, K_2SN_2**

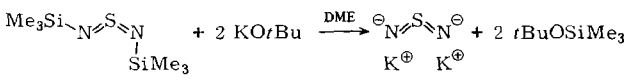
By *Max Herberhold** and *Wolfgang Ehrenreich*

Organosulfur diimides, $S(NR^1)_2$ **1**, are attacked at the sulfur by nucleophiles such as carbanions, alkoxide ions, or amide ions[1-3]. Reaction of $S(NR^1)_2$ [R^1 = $SiMe_3$ (**1a**) or *t*Bu (**1b**)] with potassium amide in liquid ammonia leads to displacement of one of the two R^1 groups with formation of salts of the type $K[NSNR^1]$ **5**[4]. More drastic reaction conditions lead to the loss of both R^1 substituents.

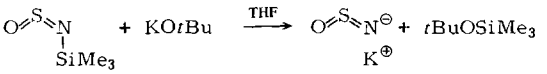


1a, R^1 = $SiMe_3$ **5a**, R^1 = $SiMe_3$ **6**
1b, R^1 = *t*Bu **5b**, R^1 = *t*Bu

We have found that the reaction of **1a** with potassium *tert*-butoxide in boiling dimethoxyethane (DME) opens up a route for preparing the pale yellow salt K_2SN_2 **6** in high yield (85–96%), thus making it a useful reagent for further syntheses. Potassium sulfinylamide, KNSO **7**, can be prepared in an analogous way[5].



1a **6**



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The salt **6** is stable up to 180 °C and above. It reacts explosively with water, methanol, or halomethanes (CH_2Cl_2, $CHCl_3$, CCl_4) thereby bursting into flames. It is insoluble in hydrocarbons, ethers, and liquid ammonia.

Table 1. Comparison of the fundamental vibrations [cm^{-1}] of the three isoelectronic 18e-systems SO_2, $NSO^{\ominus}$, and $SN_2^{2\ominus}$.

Compound	OSO [a]	**7** [b]	**6** [c]
Assignment			
ν_{as}	1360 vs	1270 vs	1198 vs
ν_s	1151 m	990 vs	1001 m
δ	518 m	515 vs	528 m

[a] Gas phase; [b] cf. [5]; [c] Nujol/Kel-F-3.

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We assume, on the basis of its very simple IR spectrum with only three absorptions (cf. Table 1), that **6** is best represented as the salt of the anion $SN_2^{2\ominus}$ (point group C_{2v}) which is isoelectronic with SO_2.

Reaction of K_2SN_2 (**6**) with chloro(trimethyl)-silane or -stannane affords the sulfur diimides $S(NSiMe_3)_2$ (**1a**) and $S(NSnMe_3)_2$ in 75 and 87% yield, respectively. The reaction of **6** with hexacarbonyltungsten leads to formation of the isocyanato complex $K[W(CO)_5(NCO)]$ **8**.

Procedure:

All operations were carried out in oven-dried apparatus under an atmosphere of dry argon; the solvents were anhydrous and saturated with argon. To 100 mL of a clear 0.79 M solution of KO*t*Bu in DME (content determined by titration with 0.1 N HCl), heated under reflux (oil bath *ca.* 95 °C), was added a solution of **1a** (8.0 g, 38.8 mmol) in DME (30 mL), dropwise within 3 h. About 15 min after starting the addition a yellow precipitate formed, the amount of which steadily increased. After completion of the addition the reaction mixture was kept at the boiling point for an additional hour. The solution was then decanted, the precipitate **6** washed with THF and ether, and dried for 3 h in a high vacuum: yield 4.6 g (85%).

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CAS Registry numbers:
1a, 18156-25-7; **6**, 82495-69-0; **7**, 73400-02-9; **8**, 82511-75-9; SO_2, 7446-09-5; $W(CO)_6$, 14040-11-0

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$K_2[Ni_2(N_2S_2)_2(CN)_2]$—A Dinuclear Complex with the $S_2N_2^{2\ominus}$ Chelate Ligand**

By *Karlheinz Hornemann* and *Johannes Weiss**

Dedicated to Professor Georg Wittig on the occasion of his 85th birthday

Mononuclear complexes of Co^{II}, Ni^{II}, Pd^{II}, and Pt^{II} with the chelate ligand $[S{=}N{-}S{-}NH]^{\ominus}$ have been known for some time. These planar complexes **1** are stable, intensely colored, and have a *cis*-configuration. They are formed as the major products in the reaction of S_4N_4 with $CoCl_2$, $NiCl_2$, $PdCl_2$, and H_2PtCl_6[1].

We have now prepared the first dinuclear complex with the dianionic chelate ligand. It is formed from **1**, M = Ni, and KCN in methanolic solution in presence of $KHCO_3$[2]; in contrast, in more alkaline media, *i.e.* in the absence of $KHCO_3$, the previously known mononuclear complex **2** is

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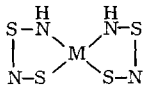
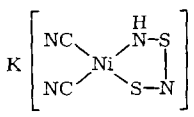
[**] Metal Sulfur-Nitrogen Compounds, Part 11.—Part 10: U. Thewalt, J. Weiss, *Z. Naturforsch. B 23* (1968) 1265.



1, M = Co, Ni, Pd, Pt



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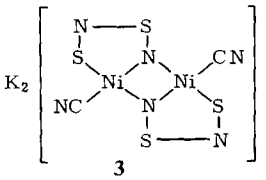

3

produced[3]. The potassium salt of the novel dinuclear complex **3**, which was characterized by elemental analysis and IR spectroscopy, is insoluble in nonpolar but soluble in polar organic solvents; aqueous solutions decompose slowly.

An X-ray crystal structure analysis was carried out on the tetraphenylarsonium salt $[Ph_4As]_2[Ni_2(N_2S_2)_2(CN)_2]$ **3a**[2] which crystallizes more readily[4].

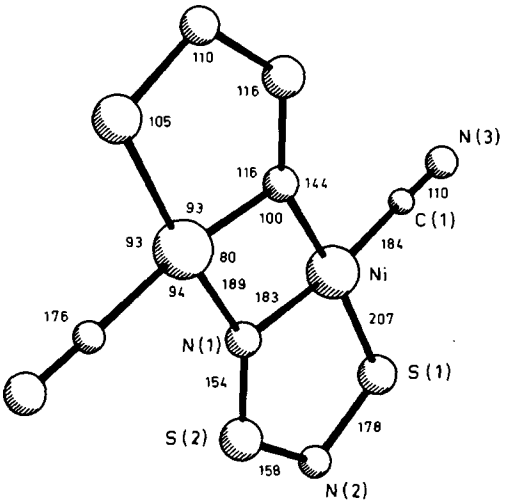

Fig. 1. Structure of the anion of **3a**. Distances in pm. The ion has a center of symmetry. All atoms, which the exception of C and N of the cyanide groups are almost coplanar; deviations of the atoms of the cyanide group from this plane: C 17 pm, N(3) 22 pm. NiNi distance 286.2(7) pm.

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[2] Procedure: **1** (490 mg, 2 mmol), KCN (260 mg, 4 mmol), and $KHCO_3$ (200 mg, 2 mmol) are refluxed for 2 h in 100 mL of methanol. The red-violet solution is filtered, concentrated, the residue dissolved in 50 mL of acetone and added slowly with stirring to 450 mL of benzene. The precipitate is filtered off and washed with benzene. Further purification was carried out by taking up the precipitate on the filter in a little methanol (≈20 mL) and treating the solution with *ca.* 200 mL of ether. The intensely violet precipitate is filtered off, washed with ether, and dried *in vacuo*. Yield 30 mg **3**. No definite melting point is observed, and the compound explodes at 239 °C. – A solution of $[(C_6H_5)_4As]Cl \cdot H_2O$ (150 mg) in 4 mL of ethanol is added to a solution of **3** (75 mg) in 40 mL of acetone. After 2 h, KCl is filtered off and the solution slowly evaporated. Violet-black, strongly intergrown crystals of **3a**, m.p. = 276 °C, are formed.

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Cleavage of S_4N_4 to S_2N_2 at Room Temperature: Formation and Structure of $(AlCl_3)_2S_2N_2$**

By *Ulf Thewalt** and *Maria Burger*

The smallest cyclic $(SN)_n$ compound, which is readily accessible by thermolysis of S_4N_4 vapor over a catalyst, is S_2N_2, whose solid-state polymerization leads to metal-like $(SN)_x$[1]. It is well known that reaction of S_2N_2 with Lewis acids such as $SbCl_5$[2a, b] or BCl_3[2c] affords isolable S_2N_2-adducts. Surprisingly, we have now been able to obtain an $S_2N_2/AlCl_3$ adduct by reaction of S_4N_4 with $AlCl_3$ at room temperature.

When a mixture of solid $AlCl_3$ and S_4N_4 is covered by a layer of CH_2Cl_2 and allowed to stand for a few days, $(AlCl_3)_2S_2N_2$ **1** is formed, along with other products, as colorless crystalline needles[3]. On contact with water or even on exposure to air the compound **1** decomposes with separation of black insoluble products. On reaction of $AlCl_3$ and S_4N_4 under conditions other than those given here, *Chan* and *Olsen*[4] obtained the S_4N_4-complex $(AlCl_3)S_4N_4$ as sole product.

The result of an X-ray structure analysis carried out for the unequivocal characterization of **1** is presented in Figure 1[5]. As in $(SbCl_5)_2S_2N_2$[2b] and in free S_2N_2[6a], the central S_2N_2-ring in **1** is completely planar. (At its center there is a crystallographic center of symmetry.) The S—N distances hardly differ from those in free S_2N_2 (1.657(1) and 1.651(1) Å[6a]). Noteworthy are the relatively short S...Cl contacts.

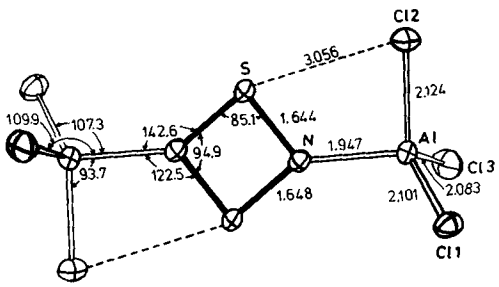

Fig. 1. Structure of the $(AlCl_3)_2S_2N_2$ complex in the crystal, with bond lengths [Å] and angles [°]. Errors in the S—N, Al—N, and Al—Cl bond lengths: 0.003, 0.003, and 0.002 Å, respectively; errors in the bond angles at S, N, and Al: 0.2, 0.2, and 0.1°, respectively. Deviations from the S_2N_2 plane: Al 0.004 Å, Cl2 −0.087 Å.

Symmetrical cleavage of the S_4N_4 cage with formation of neutral S_2N_2 rings evidently proceeds quite readily and can be preparatively exploited if—firstly—a Lewis acid which has the ability to combine with both S_4N_4 as well as S_2N_2 is present and—secondly—if the solubilities of the individual compounds are such that the S_2N_2-adduct crystallizes out. These prerequisites are fulfilled in the case of $AlCl_3$ in CH_2Cl_2. The same applies for the system $CuCl_2/S_4N_4$ in acetonitrile; in this case the polymeric complex

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$[Cu(CH_3CN)Cl_2]_2S_2N_2$ can be isolated, which likewise contains neutral S_2N_2 groups as bridging ligands[6b].

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[2] a) R. L. Patton, W. L. Jolly, *Inorg. Chem. 8* (1969) 1389; b) R. L. Patton, K. N. Raymond, *ibid. 8* (1969) 2426; c) R. L. Patton, W. L. Jolly, *ibid. 8* (1969) 1392.
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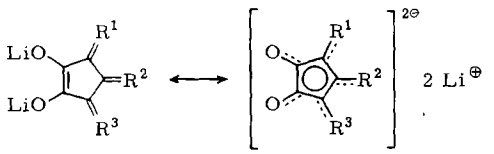
Electrochemical Oxidation of Croconate Salts; Evidence of the Chemical Equivalence of the Carbonyl Oxygen Atom and the Dicyanomethylene Group**

By *Lawrence M. Doane* and *Alexander J. Fatiadi**

We have found that dicyanomethylene derivatives of croconates [pseudooxocarbon compounds of general formula $C_nO_m[C(CN)_2]_{n-m}^{r-}$][1] are excellent models for testing the concept of *Wallenfels*[2] on the chemical equivalence of carbonyl oxygen and the dicyanomethylene group. Several electrochemical studies have been carried out on aromatic oxocarbon[3a] and pseudooxocarbon compounds[3b], but, as yet, no reversible electron transfer reactions have been reported for croconates. We report here: (i) on some cyclovoltammetric and ESR investigations of salts of the oxocarbon dianion, croconate **1**, and the pseudooxocarbon dianions[4], 3-(dicyanomethylene)croconate **2**, 3,5-bis(dicyanomethylene)croconate [croconate violet] **3**, and 3,4,5-tris(dicyanomethylene)croconate [croconate blue] **4**; (ii) on the first supporting electrochemical evidence for the postulated chemical equivalence of $=O$ and $=C(CN)_2$.



1, $R^1=R^2=R^3=O$
2, $R^1=R^3=O$, $R^2=C(CN)_2$
3, $R^2=O$, $R^1=R^3=C(CN)_2$
4, $R^1=R^2=R^3=C(CN)_2$

Figure 1 shows cyclic voltammograms of the salts of **1**–**4** in *N,N*-dimethylformamide (DMF) containing 0.5 mol/L tetraethylammonium perchlorate (TEAP); the peak potentials are given in Table 1. The general behavior of dianions of **1**–**4** is similar and is characterized by essentially equal anodic and reversal cathodic peak currents and a peak potential separation ($E_{pa}-E_{pc}$) of 0.06–0.07 V. These results suggest a reversible one-electron oxidation of the dianion to a stable radical anion followed by a reversible one-electron oxidation of the radical anion to the neutral molecule. At scan rates less than 20 mV/s, the more positive cathodic wave of the dianion of **4** is very small, indicating a fast chemical reaction following the electron transfer.

Thin-layer cyclic voltammetry provides further evidence of the electrochemical reversibility and the stability of the components of the redox couple[5]. If scan reversal occurs immediately after the first oxidation wave, essentially equal anodic peak and reversal cathodic peak currents are obtained for all dianions. The stability of the radical anion is therefore no less than several minutes. Equal anodic and cathodic peak currents are obtained at the second redox couple of the dianion of **1**. However, for dianions of **3** and **4**, scan reversal after the second oxidation wave gives no cathodic wave where reversible reduction of the neutral species and the radical anion should each occur. For the dianion of **2**, three cathodic waves appear on reversal after the second oxidation wave. Despite the results of cyclic voltammetry this indicates that the neutral species [except in the case of **1**] undergo chemical transformations that alter their cathodic waves.

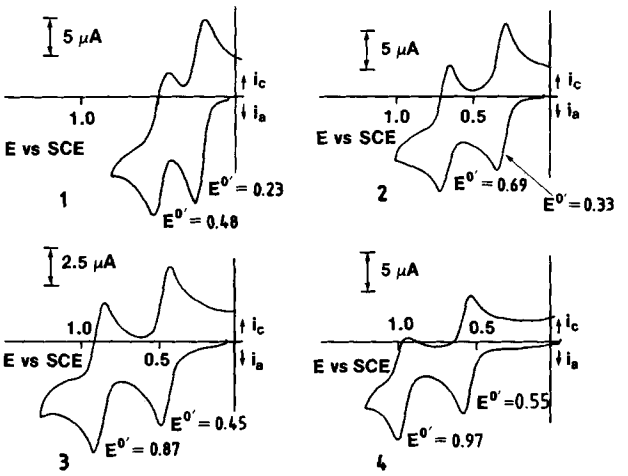


Fig. 1. Cyclovoltammograms of the dianions **1**–**4**. For conditions see Table 1.

Table 1. Cyclovoltammometric data for the oxidation of croconates in DMF [a]. E [V] *vs.* SCE.—In the case of **1**–**4** two reduction steps were observed in each case (E_{pc1}, E_{pc2} [V] *vs.* SCE): **1**: −0.78, −1.21; **2**: −0.68, −0.88; **3**: −1.48, −1.73; **4**: −1.05, −1.40. Except in the case of **4**, the reductions were reversible.

Dianion of	1. Peak [b] E_{pa}	E_{pc}	ΔE_p	2. Peak [b] E_{pa}	E_{pc}	ΔE_p
1	0.26	0.20	0.06	0.51	0.44	0.07
2	0.36	0.30	0.06	0.72	0.66	0.06
3	0.48	0.41	0.07	0.90	0.83	0.07
4	0.58	0.51	0.07	1.00	0.94 [c]	0.06

[a] Concentration of TEAP 0.5 mol/L. Working electrode: gold disk with surface area of 0.079 cm^2 (in the case of **3**: 0.051 cm^2), sweep rate 0.05 V/s. [b] E_{pa} and E_{pc} are the anodic and cathodic peak potentials, respectively. [c] Weak current on scan reversal.

Evidence of radical anion formation was obtained from ESR spectra of dianion solutions electrooxidized in DMSO at a potential approximately 100 mV more positive than the peak potential of the first oxidation wave. The ESR spectrum of the electrooxidized solution of the salt **3** shows a 9-line pattern, which possibly indicates interac-

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tion of the unpaired electron with four magnetically equivalent nitrogen atoms ($a^N = 5.2$ G). The half-life of the radical anion is *ca.* 100 minutes. *Russell* and *Osuch*[6] have shown that the ESR spectrum of the 1,2-cyclopentanesemidione radical is a symmetrical pentet; the unpaired electron is delocalized over the semidione group. The 9-line pattern of the radical anion of **3** indicates that the unpaired electron is delocalized over the dicyanomethylene group and the oxygen atoms.

Wallenfels[2] has proposed that the dicyanomethylene group and the oxygen atom are chemically analogous and that substitution of one group for the other merely reflects a change in electronegativity. The potential of the first oxidation wave increases linearly by *ca.* 100 mV on addition of each dicyanomethylene group [see **1**—**4** in Table 1 and Fig. 1]; *i.e.* the electrochemical oxidation becomes increasingly difficult in the series **1**—**4**. This linearity and the delocalization in the radical anions indicate that the inductive effect of each dicyanomethylene group is independent of the other and independent of the position in the ring. Clearly a linear change in electronegativity of the substituting dicyanomethylene group supports *Wallenfels*' concept of chemical equivalency of =O and $=C(CN)_2$.

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1, 66888-97-9; **2**, 82457-05-4; **3**, 82457-06-5; **4**, 82457-07-6.

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[3] a) M. Fleury, P. Souchay, M. Gouzerh, *Bull. Soc. Chim. Fr. 1968*, 2562; F. Arcamone, C. Prevost, P. Souchay, *ibid. 1953*, 891; b) S. Hünig, H. Pütter, *Chem. Ber. 110* (1977) 2524, 2532; G. Seitz, *Nachr. Chem. Tech. Lab. 28* (1980) 804.

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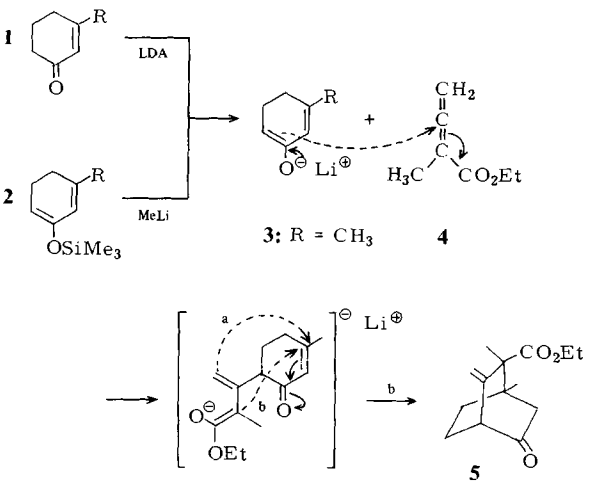
Bicyclo[2.2.2]octanes from Allenecarboxylic Acid Esters and Cyclohexadienolates

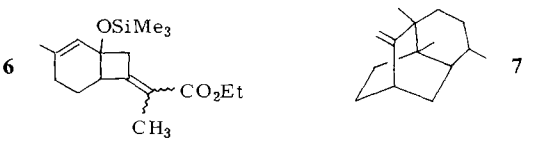
By *Dietrich Spitzner**

Cyclohexenones such as **1** can be selectively deprotonated in a kinetically controlled reaction with lithiated bases such as lithium diisopropylamide (LDA) to give lithium cyclohexadienolates of type **3**. Compounds **3** react with acrylic acid esters in what may be formulated as a Diels-Alder cycloaddition or Michael cascade reaction to give 5-oxobicyclo[2.2.2]octane-2-carboxylic acid esters, exclusively in the *endo*-form[1a].

Allenecarboxylic acid esters are capable of undergoing [2+2]- as well as [4+2]-cycloadditions; Lewis acids accelerate both reactions, but decisively improve the *endo* selectivity only in the case of the [2+2]-cycloaddition[1b]. We have now reacted the allenecarboxylic acid ester ethyl 2-methyl-2,3-butadienoate **4**[2] with **3** in amine-free medium and obtained isomer-free (capillary-GC/MS) ethyl 1,2-dimethyl-3-methylene-5-oxobicyclo[2.2.2]octane-2-carboxylate **5**[3] (Route b).



The high *endo*-selectivity of the addition is noteworthy also in this example. However, although acrylic acid esters react with both cyclohexadienolates of type **3** as well as with the corresponding trimethylsiloxycyclohexadienes **2** to give 5-oxobicyclo[2.2.2]octane-2-carboxylic acid esters, allenecarboxylic acid esters such as **4** form the bicycles **5** only on reaction with **3**; with trimethylsiloxy-activated



dienes such as **2** they undergo polar [2+2]-cycloaddition to give mainly cyclobutylideneacetic acid esters (*e.g.* **6**)[4]. Both **5** as well as analogous bicyclo[2.2.2]octanes are suitable educts[5] for the synthesis of tricyclic sesquiterpenes such as seychellene **7**.

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2, 54781-27-0; **3**, 78070-27-6; **4**, 5717-41-9; **5**, 82432-15-3

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[3] **5**: A solution of **3** (prepared from **2**, R = CH_3, and a 5% solution of methyllithium in ether at −60 °C under argon) in tetrahydrofuran-ether (*ca.* 4:1) is treated dropwise within 10 min at −60 °C with 1.1 equivalents of **4**. The reaction mixture, which is initially yellow and later turns orange-red, is kept at this temperature for 3 h and then warmed to −20 °C. After 12 hours' stirring at −20 °C the mixture is worked up (acidification with 1M HCl, ether extraction, drying of the organic phase over $MgSO_4$) and distilled in a Kugelrohr (100—110 °C/0.01 torr). **5** is obtained as a colorless oil (yield 75%), which crystallizes on cooling in a refrigerator (m.p. 65 °C). EI-MS: *m/z* 236 (M^+, 18%); 250 MHz ^{1}H-NMR ($CDCl_3$): $\delta = 5.05$, 4.82 (s, 2 olefin-H), 4.18—4.06 (q, $J = 7$ Hz, on AB, $J_{AB} = 11$ Hz, diastereotopic ester-CH_2, 2H), 2.99 (t, $J = 3$ Hz, 1 bridgehead-H), 2.86, 2.79 (d, $J = 3$ Hz, on A part of an AB, $J_{AB} = 19$ Hz, 1H), 2.05, 1.97 (B part, $J_{AB} = 19$ Hz, 1H), 1.95—1.85 (m, 3H), 1.47 (s, CH_3), 1.43—1.31 (m, 1H), 1.22 (t, $J = 7$ Hz, ester-CH_3), 0.99 (s, bridgehead-CH_3); 62.9 MHz ^{13}C-NMR ($CDCl_3$): $\delta = 210.8$ (s, ketone-C), 173.9 (s, ester-C), 149.2 (s), 111.4

(t), 60.6 (t), 54.5 (d), 52.4 (s), 49.0 (s), 38.4 (s), 29.3 (t), 23.7 (t), 21.4 (q), 21.2 (q), 13.8 (q).
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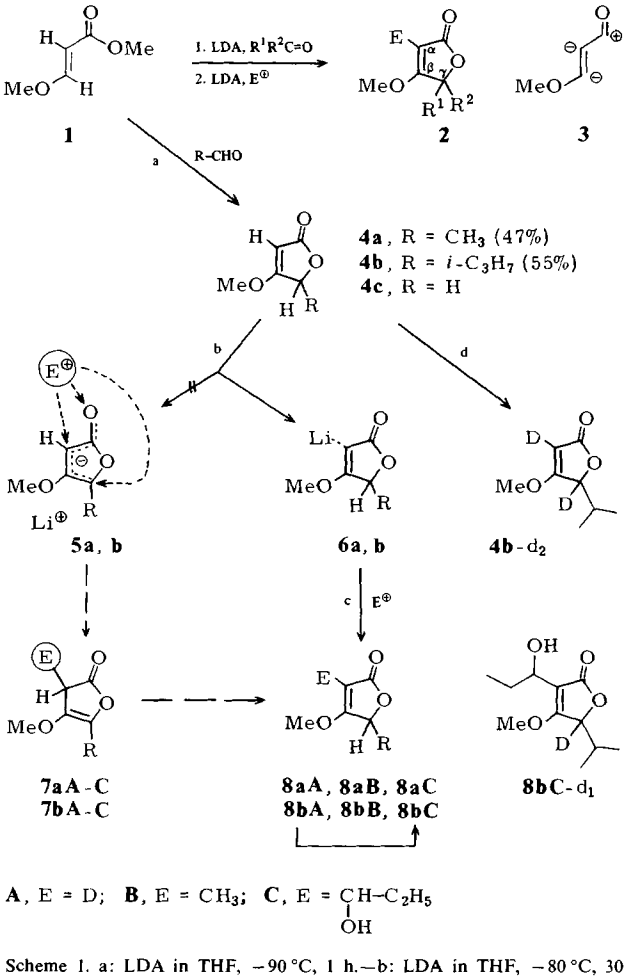
Kinetic Acidity of Methine Protons and Carbonyl-Activated Methylene Protons**

By *Okiko Miyata* and *Richard R. Schmidt**

We have introduced the substituted acrylic ester **1** as a versatile synthon **3**[1]. Hence, the α,γ,γ-trisubstituted γ-lactones (tetronates) **2** could be synthesized from **1** in two steps[2,3]; by means of acetaldehyde and isobutyraldehyde the γ-substituted lactones **4a** and **4b** were synthesized in a one-step reaction (Scheme 1).



Scheme 1. a: LDA in THF, −90 °C, 1 h.—b: LDA in THF, −80 °C, 30 min.—c: 40 min at −80 °C, 30 min at −50 °C; yield: quant. **8aA**, 61% **8aB**, 48% **8aC**, quant. **8bA**, 68% **8bB**, 56% **8bC**.—d: 1 M NaOMe in MeOD, R. T., 20 h; yield: quant. **4b**-d_2.

After deprotonation, the parent compound **4c**—as found by *Pelter et al.*[4]—reacts with electrophiles in aprotic media at the γ-carbon atom or at the carbonyl oxygen atom. Surprisingly, the α-substituted products **8aA**—**8aC** and **8bA**—**8bC** were obtained from **4a** and **4b** after deprotonation with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) and reaction with CH_3OD, CH_3I, or C_2H_5CHO. These products could also have arisen from the γ-deprotonated species **5a** and **5b** *via* **7aA**—**7aC** and **7bA**—**7bC**; to exclude this route **8bA** was deprotonated and treated with propionaldehyde; following work-up with D_2O, however, no **8bC**-d_1 was formed.

In consequence, direct lithiation of **4a** and **4b** to afford **6a** and **6b**, respectively, must be assumed. Rapid H/D exchange in basic protic media was established through formation of **4b**-d_2 from **4b** in NaOMe/MeOD.

These investigations show that in the LDA/THF system the kinetic acidity of the α-vinyl protons of **4a** and **4b** is greater than that of the carbonyl-activated γ-methylene protons, although abstraction of the latter would lead to the resonance-stabilized oxapentadienyl anions **5a** and **5b**, respectively. This result emphasizes the importance of the direct deprotonation of inductively activated vinylic methine groups; of course, it is also important that the metalated species can be intramolecularly complexed[1].

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A 2,6-Diazasemibullvalene**

By *Christoph Schnieders, Hans-Josef Altenbach* and *Klaus Müllen**

In the extreme case, lowering the energy barrier for the degenerate Cope rearrangement in bullvalene, barbaralane, and semibullvalene systems leads to a "bishomoconjugated" ground state[1]. According to theoretical considerations[2], a ground state of this type occurs in semibullvalenes in which the CH groups in the 2- and 6-, or 3- and 7-, positions have been replaced by N atoms[3]. We have now succeeded in synthesizing the first diazasemibullvalene with which we have been able to test the predictions experimentally.

Our studies of the bisallyl system **3**, which we obtained from the semibullvalene **1**[4] by reductive cleavage of the σ-bond[5], indicated that the readily accessible diaza analogue **4** and the dihydro derivative **5**[6] were suitable precursors for **2**. **5** reacts with *N*-bromosuccinimide to afford a mixture of the mono-, di-, and tribromides **6**—**8**; according to the spectral data **7** is configurationally uniform.

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[**] Vinyl Carbanions, Part 15. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. *O. M.* expresses thanks to the Alexander-von-Humboldt-Stiftung for financial support.—Part 14: [2].

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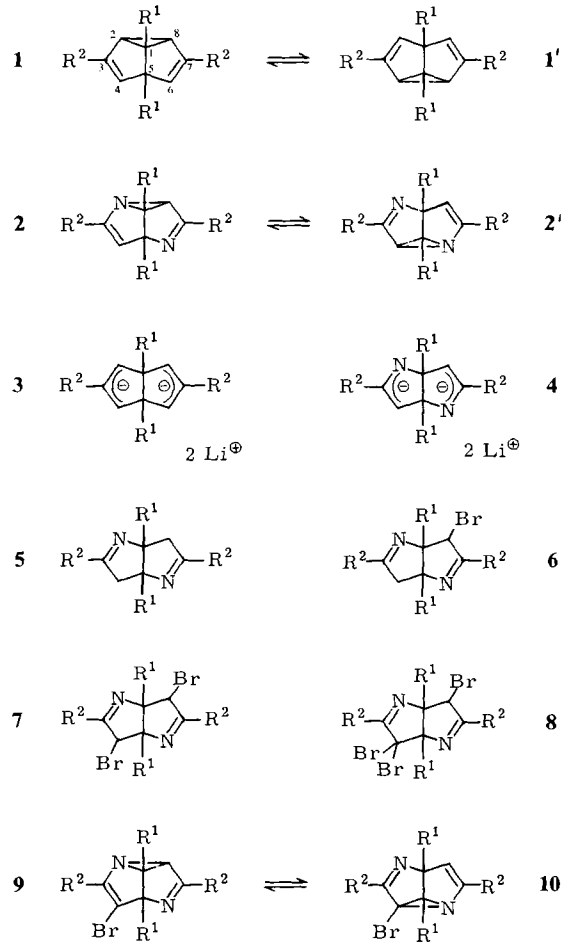
[**] This work was supported by the Fonds der Chemischen Industrie. We thank Priv.-Doz. Dr. J. J. Veith, TH Darmstadt, for the FD-MS measurements.



$R^1 = CH_3$, $R^2 = Ph$

The reductive elimination of **7** (lithium, [D_8]tetrahydrofuran (THF), −78 °C), which was monitored by NMR spectroscopy, led within a few seconds to **2**: elemental composition (FD-MS) confirmed that both bromine atoms had been cleaved off.

Just as in **7**, the number of ^{1}H- and ^{13}C-NMR signals [^{1}H-NMR ([D_8]THF, 300 MHz, −30 °C): $\delta = 1.43$ (1-CH_3, 5-CH_3); 5.50 (H-4, H-8); 7.67 (H-*o*-phenyl); 7.22 (H-*m*,*p*-phenyl); ^{13}C-NMR ([D_8]THF, 75.5 MHz, −30 °C): $\delta = 80.2$ (C-1, C-5); 15.6 (1-CH_3, 5-CH_3); 152.7 (C-3, C-7); 99.4 (C-4, C-8); 135.6 (quart. C-phenyl), 129.7, 129.0, 127.5 (C-phenyl)] confirm the existence of an effective C_2 axis which arises on the NMR time scale because of the rapid degenerate Cope rearrangement **2** ⇌ **2′**. The position of the signals from C-4 and C-8 ($\delta = 99.4$), as well as that from H-4 and H-8 ($\delta = 5.50$) is in accord with an averaged olefin and aziridine "environment".

As expected for a degenerate Cope rearrangement **1** ⇌ **1′**, the ^{13}C-NMR signal (75.5 MHz) for C-4 and C-8 at −90 °C in the semibullvalene **1** experiences a pronounced line broadening (width at half-height $\Delta_{1/2} \approx 570$ Hz). Under the same conditions, the corresponding signal of the diaza analogue **2** exhibits no broadening ($\Delta_{1/2}(-90\,°C) = 5$ Hz). We attribute this to a drastic increase in the rate of the Cope rearrangement and not to the existence of a bishomoconjugated ground state, since the signal becomes broader upon lowering the temperature further ($\Delta_{1/2}(-120\,°C) = 19$ Hz).

Debromination of the tribromide **8** leads to formation of the monobromosemibullvalene **9** ⇌ **10** [^{1}H-NMR ([D_8]THF, 300 MHz, −30 °C): $\delta = 1.52$, 1.45 (1-CH_3 and 5-CH_3, respectively); 5.12 (H-8); 7.30–7.90 (H-phenyl); ^{13}C-NMR ([D_8]THF, 75.5 MHz, −30 °C): $\delta = 76.1$, 84.3 (1-CH_3 and 5-CH_3, respectively); 14.5, 15.7 (1-CH_3 and 5-CH_3, respectively); 144.6, 158.8 (C-3 and C-7, respectively); 112.8 (C-4); 79.1 (C-8); 135.0 (quart. C-phenyl); 134.6 (quart. C-phenyl), 128.3–130.9 (C-phenyl)]. The ^{13}C chemical shifts suggest a valence isomerism[3,4] **9** ⇌ **10** with **9** as the predominant form.

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1, 32139-60-9; **2**, 82445-03-2; **3**, 82456-98-2; **4**, 82445-04-3; **5**, 82445-05-4; **6**, 82445-06-5; **7**, 82445-07-6; **8**, 82445-08-7; **9**, 82445-09-8; **10**, 82445-10-1.

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[5] C. Schnieders, W. Huber, K. Müllen, unpublished results. Prof. Dr. *J. Sauer* (Regensburg) is thanked for supplying compound **1**.
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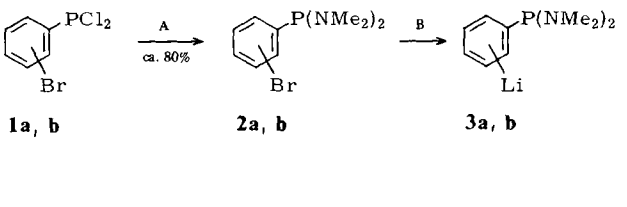
o- and *m*-Phenylenebis(dichlorophosphane)—Versatile, Useful Synthetic Building Blocks

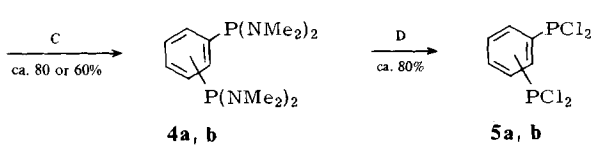
By *Kurt Drewelies* and *Hans Peter Latscha**

Dedicated to Professor Georg Wittig on the occasion of his 85th birthday

Of the possible phenylenebis(dihalophosphanes) only the *p*-phenylene compounds have been described so far[1]. We have now been able to synthesize and purify *o*- and *m*-phenylenebis(dichlorophosphane) **5a** and **5b**, respectively. The syntheses (Scheme 1) *via* the novel intermediates **2**, **3**, and **4** proceed in good yields at each stage.



1a, b **2a, b** **3a, b**



4a, b **5a, b**

Scheme 1. **a**: *ortho*, **b**: *meta*. A: Et_2O, Me_2NH until saturated; B: Et_2O, BuLi in *n*-hexane; C: Et_2O, $ClP(NMe_2)_2$ in Et_2O (isolation of **3** not necessary); D: Et_2O, HCl gas. All operations were performed with rigorous exclusion of moisture under argon.

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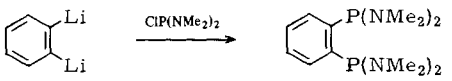
4a is also formed as the main product of the reaction of *o*-dilithiobenzene **6** with chlorobis(dimethylamino)phosphane in ether solution.



6 **4a**

The colorless substances **3a** and **5b** are liquids at room temperature and extremely sensitive towards hydrolysis. **5a**: b.p. = 97–99 °C/10^{-3} torr, ^{13}C-NMR ($CDCl_3$): δ = 144.2 (t), 133.5 (s), 130.6 (t); *m/z* 278 (M^+). **5b**: b.p. = 89–91 °C/10^{-3} torr; ^{13}C-NMR ($CDCl_3$): δ = 141.7 (dd), 134.2 (d), 131.7 (t), 129.8 (t); *m/z* 278 (M^+).

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1a, 5274-51-1; **1b**, 5590-57-8; **2a**, 82495-63-4; **2b**, 82495-64-5; **4a**, 82495-65-6; **4b**, 82495-66-7; **5a**, 82495-67-8; **5b**, 82495-68-9; Me_2NH, 124-40-3; $ClP(NMe_2)_2$, 3348-44-5

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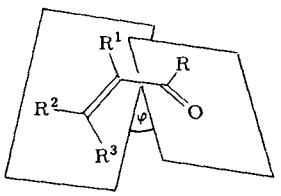
Determination of the Conformation of Acyclic α,β-Unsaturated Aldehydes and Ketones from Their Infrared and Raman Spectra—Results and Limitations of Model Calculations**

By *Hans-Joachim Oelichmann, Daniel Bougeard,* and *Bernhard Schrader**

The α,β-unsaturated aldehydes (R = H) and ketones (R = alkyl) **1** may exist in two planar conformations, the *s-cis* ($\varphi = 0°$) and the *s-trans* conformation ($\varphi = 180°$), as well as in non-planar conformations.



1

Of the spectroscopic methods available, for the determination of the dihedral angle φ IR and Raman spectroscopy would appear to be especially suitable. Known empirical observations[3,8] were extended by model calculations[11] of the frequencies and IR and Raman intensities of *s-cis-* and *s-trans*-acrolein, *trans-* and *cis*-crotonaldehyde, methacrolein, and *s-cis-* and *s-trans*-methyl vinyl ketone[12,13]. The transferable sets of force constants determined thereby enabled calculation of the frequencies of a model molecule **1**, R, R^1, R^2, R^3 with point masses, m = 15, for $\varphi = 0, 30, \ldots 180°$. Furthermore, we have calculated the IR and Raman intensities of methyl vinyl ketone for $\varphi = 0, 30, \ldots 180°$. These model calculations together with old and new experimental data allow the following general conclusions to be drawn from the IR and Raman spectra of **1**:

In the IR and the Raman spectrum the frequency of the C=O stretching vibration is greater than 1670 cm^{-1} and that of the C=C stretching vibration lower than 1670 cm^{-1}; the vibrational energy is located to 65–85% on the bond in question. Despite conjugation the coupling of the C=O and C=C vibrations is smaller than 10%; as is the case for conjugated dienes[15], in the *s-trans* conformers the vibration with the higher frequency has in-phase character, whereas the reverse is true for the *s-cis* conformers.

It emerges that the relative values of the C=O and C=C frequencies and the integral intensities, which are readily accessible from the spectra, provide more information than the absolute values about the dihedral angle φ. Table 2 contains limiting and mean values.

Table 2. General IR and Raman characteristics for the determination of the conformation of α,β-unsaturated ketones and aldehydes [3, 7, 8, 12, 13].

	s-cis	*s-trans*
$\Delta\tilde{\nu} = \nu(C{=}O) - \nu(C{=}C)$	> 60 (≈ 68)	< 60 (≈ 40)
IR intensity $A_{C-O}/A_{C=C}$	< 2.6 (≈ 1.4)	> 2.6 (≈ 5.2)
Raman intensity $I_{C-O}/I_{C=C}$	< 0.5 (≈ 0.25)	> 0.5 (≈ 0.7)
Depolarization ratio ρ(C=O) (Raman)	> 0.3 (≈ 0.4)	< 0.3 (≈ 0.2)

Model calculations of the frequencies and IR and Raman intensities for particular molecules can provide more definite information about the conformation. An accurate determination of the dihedral angle φ is, however, not yet possible; on the one hand because of the inadequacy of the semiempirical quantum chemical methods required for the intensity calculation and, on the other, because of the unbearable expense of *ab initio* methods.

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Chemistry of Coal Utilization, Second Supplementary Volume. Edited by M. A. Elliot, Wiley-Interscience, New York 1981. 2374 pages, bound, $ 165.00.

The American "Chemistry of Coal Utilization", a handbook that has already become a classic and that is certainly unique in its scope and treatment of the material, has now been updated by the appearance of the second supplementary volume, after the original two-volume work of 1945, edited by *H. H. Lowry*, was first supplemented in 1963. As in the case of the previous volumes, a committee of the National Research Council of the U.S. National Academy of Sciences assumed the sponsorship of the new supplementary volume which, under the new editor *Elliot—Lowry* died ten years ago—includes contributions from 60 well-known authors. In continuation of the earlier work, detailed information is given not only on coal chemistry in the narrower sense but also, with the exception of mining technology, on all technologies for the utilization and upgrading of coal and on the conversion of coal into energy, fuels, and chemical raw materials. In spite of the primary aim to take up the story at the point at which the review of the first supplementary volume ended, *i.e.* essentially to give a critical review of the literature between about 1958 and the second half of the seventies and to describe further developments in this period, to a large extent the result has been an almost textbook-like account rather more suitable for advanced readers. Specifically, the 31 chapters deal with the coal industry, coal research and development (an overview written by the editor himself); coal resources (only the deposits of the United States are treated in detail); origin, petrography, and classification of coal; physical properties of coal and coal products; mechanical properties; plastic properties; analysis of coal, trace elements, and mineral constituents; chemical reactions and chemical constitution of coal; transport, storage, and handling; preparation; briquetting; pyrolysis and hydropyrolysis (3 chapters); solid pyrolysis products; coar tar (2 chapters); coke-oven gas; combustion of coal (2 chapters); coal ash—its effect on combustion; control of pollution from combustion processes; gasification of coal (3 chapters); underground gasification of coal; liquefaction of coal (3 chapters); conversion of coal and coal gases into fuels, chemicals, and other products; and environmental, health, and safety implications of increased coal utilization.

On the whole, it must be said that the compilation and organization of the enormous volume of material has been highly successful. Overlapping between individual chapters, unavoidable because closely related subjects are treated by different authors, is kept to reasonable limits. The reviewer is not in a position to judge to what extent it has been possible to take into account the literature and all the developments of the various technologies. After all, the quality of the contribution depends in the final account on the knowledge, experience, and carefulness of the particular author (information about the professional career and the present position of each author is given by brief biographies at the beginning of the chapters). Apart from some contributions from the United Kingdom, Australia, and the German Federal Republic, the majority of the chapters have been written by American authors. In reading some chapters one cannot quite escape the (subjective) impression that the account, particularly of the economic and technical developments, is frequently limited substantially to the situation in the United States. For example, in Chapter 28 (Liquefaction Processes) all the American processes for direct liquefaction of coal are described in detail, whereas there is nothing about the corresponding developments of the National Coal Board in the United Kingdom and there are only a few lines on the IG-"Neu" Process in Germany, by which is meant the new activities in connection with the hydrogenation of coal, based on the old IG process. A partial explanation for this shortcoming may be that these European developments really started up only in the mid-seventies, not long before the early editorial deadline (depending on the chapter, between August 1976 and the end of 1978). Other examples could be quoted. Another point of criticism relates to the use of units: it must be just as annoying for the English or American reader when, for example as on page 1782, temperatures are given in degrees Fahrenheit and enthalpies in Btu/lb-mole in one place and four pages later the same author uses the units Kelvin and kcal/g-mole!

The extensive subdivision of the text by headings makes for clarity, the graphic presentation including the figures and tables is excellent, and the citation of references in footnotes on the same page is exemplary. Small mistakes and printing errors do not appear to exceed the usual quota. The subject index, however, leaves something to be desired.

All in all, this second supplementary volume in combination with the earlier work offers a unique compilation, of inestimable value, of the scientific and technical literature on coal. No library should therefore delay in getting this supplement to their "Lowry". But even without the earlier volumes, which, by the way, can still be obtained as reprints, the book will be highly valuable for the interested specialists, if not indeed indispensable.

Matthias W. Haenel [NB 562 IE]

Protective Groups in Organic Synthesis. By *T. H. Green*. John Wiley & Sons, Chichester 1981. xiii, 349 pp., bound, £ 26.25.

Although the use of protective groups for the blockage (deactivation and differentiation) of functional groups is indispensable in many organic reactions, particularly in special classes of substances such as the carbohydrates and the amino acids, in the planning of a particular synthesis one should always bear in mind that this advantage is accompanied by a drawback: Two additional reaction steps

are usually necessary, for the protective groups must first be introduced and then removed. A large number of protective groups have been proposed for a variety of purposes, differing in the nature of their introduction, their differentiated removal, their stability to special reagents, *etc.*, and frequently capable of being used for only one reaction step. Thus, recently, protective groups that can be removed photochemically or electrochemically have been called upon. The fact that, after the widely used book by *McOmie* (1973), another book on protective groups has now appeared, in which the modern developments in this field have been particularly taken into account, is highly welcome.

A short introduction on the importance of protective groups in organic chemical synthesis is followed by a description, in six chapters, of about 400 protective groups for the important functional groups. The following protective groups are discussed in detail: monohydroxy compounds: substituted alkyl ethers (42), silyl ethers (12), and esters (52); 1,2- and 1,3-diols: acetals and orthoesters (31); phenols: ethers, esters, carbonates, carbamates, and sulfonates (32); carbonyl compounds: full acetals, thioacetals, hemithioacetals, *O*-substituted cyanohydrins, substituted hydrazones, imines, oxazolidines, imidazolidines, and thiazolidines (37). (The monoblockage of dicarbonyl compounds is also described here (7).) Carboxy compounds: esters, amides, and hydrazides (63); thiols: thioethers (28), thioesters (9), disulfides (2) and sulfenyl derivatives (2); amines: carbamates, amides, imides, *N*-alkyl compounds, aminoacetals, imines, enamines, *N*-metal compounds, and *N*-heteroatom derivatives (91). There is no information on the protective groups for olefinic double bonds.

For the individual protective groups the processes of their formation and removal are described, always with references to the literature and, wherever possible, with special observations (range of application, stability, *etc.*). No information is given on the availability or synthetic accessibility of the reagents used.

A particularly valuable feature of the book is Chapter 8, "Reactivities, Reagents, and Reactivity Charts," in which the stability of many of the protective groups described in the book with respect to 108 prototype reagents from 16 reaction areas (*e.g.* oxidation, reduction, and organometallic reactions) is summarized in tabular form. For example, it can be deduced from the tables that *tert*-butyl diphenylsilyl ethers are still stable at pH 2–4, while the *tert*-butyl dimethylsilyl ethers are already cleaved in this pH range.

The book is arranged systematically; however, because of the wealth of information, the reader will need some time to become familiar with its use.

This could have been avoided by selecting three to five "standard protective groups" supplementing one another for each of the individual functionalities, that would ensure success in 80–90% of the cases. It would then have been possible to include experimental instructions for the formation and the removal of these standard groups. Some description of the elegant methods for the blocking and activation of functionalities, *e.g. via S-* or *O*-acetals, would also have been desirable.

In conclusion, the book will undoubtedly prove very useful for the synthetic chemist both in industry and academic circles, and it can be expected to find wide use.

Lutz-F. Tietze [NB 568 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 (Federal Republic of Germany).

Chemical Additives for Fuels. Developments since 1978. Edited by *M. T. Gillies*. Noyes Data Corporation, Park Ridge, New Jersey 1982. xii, 308 pp., bound, $ 48.00.—ISBN 0-8155-0886-7

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Fourier, Hadamard and Hilbert Transforms in Chemistry. Edited by *A. G. Marshall*. Plenum Press, New York 1982. xii, 562 pp., bound, $ 65.00.—ISBN 0-306-40904-6

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Charakterisierung von Kunststoffen mit physikalischen Methoden. Verfahren und praktische Anwendung. By *G. Kämpf*. Carl Hanser Verlag, München 1982. 331 pp., bound, DM 78.00.—ISBN 3-446-13382-8

Carbocationic Polymerization. By *J. P. Kennedy* and *E. Maréchal*. John Wiley & Sons, Chichester 1982. ix, 510 pp., bound, £ 55.50.—ISBN 0-471-01787-6

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Technische Chemie I. Grundverfahren. By *W. Brötz* and *A. Schönbucher*. Verlag Chemie, Weinheim 1982. xv, 380 pp., bound, DM 68.00.—ISBN 3-527-25852-3

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The Chemistry of Pesticides. Their Metabolism, Mode of Action and Uses im Crop Protection. By *K. A. Hassall*. Verlag Chemie, Weinheim 1982. xiv, 372 pp., bound, DM 148.00.—ISBN 3-527-25969-4

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Theoriewandel in der Wissenschaftsgeschichte. Chemie im 18. Jahrhundert. By *E. Ströker*. V. Klostermann, Frankfurt 1982. viii, 324 pp., bound, DM 68.00.—ISBN 3-465-01497-9

Der Schutz wissenschaftlicher Forschungsergebnisse. By *F.-K. Beier* and *J. Straus*. Verlag Chemie, Weinheim 1982. viii, 116 pp., bound, DM 48.00.—ISBN 3-527-25940-6

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Signal Substances and their Reception in the Sexual Cycle of Marine Brown Algae

By Lothar Jaenicke* and Wilhelm Boland

Dedicated to Professor Hermann Schildknecht on the occasion of his 60th birthday

Attraction and repulsion are responses to chemical stimuli which can be received and processed even by unicellular organisms without a morphologically defined nervous system. Chemical substances trigger off a chain of events which starts with a membrane-bound signal receptor and, after a sequence of regulatory and modulatory steps, ends in the modulation of a motor effector organ. Binding of the signal substances to the receptor produces conformational changes in which the receptor subunits are mutually dependent on one another, and also leads to chemical modification of the subunits and affects their molecular activity. These interactions, together with the characteristic type of movement, result in a physiological pattern of behavior which enables the flagellated sex cells (gametes) of marine brown algae to finally locate their partners. The simple but highly specific brown algae gamete systems have been investigated structurally and their biological activity analyzed. The signal substances are mainly highly unsaturated aliphatic or cyclic hydrocarbons with unsaturated side chains (general formula *e.g.* $C_{11}H_{14}$, $C_{11}H_{16}$, $C_{11}H_{18}$). These systems also serve as a simplifying model which helps in the understanding of complex ganglionic pathways in higher living organisms where the sense organs convey information from the surroundings to the central nervous system through nerve pathways. The information is then processed and answered, *via* efferent pathways, as movement.

1. Introduction

Communication by means of chemical signals made an early appearance in the history of evolution. Even bacteria are equipped for the reception and processing of signals to enable them to find a suitable environment; these systems have been studied biochemically in great detail[1]. Ciliates prepare for copulation by means of a chemical information system whose components are known, but whose mode of action remains to be elucidated[2]. The pheromone system of insects is extremely sensitive; it was first investigated in the classical studies of *Butenandt et al.* on the silkmoth and has since been studied extensively by chemists and sensory physiologists[3]. These systems have given considerable insight into the way in which signals are transmitted from the nerve cells to the central nervous system. Vertebrates are not inferior to insects in this respect. One only needs to think of the remarkably sensitive olfactory organs of fish, the tracking capabilities of dogs, and other similar phenomena known to nature watchers and hunters. Such signal sequences came to be expected in mobile organisms which require specific instructions when searching for food or sexual partners, for brood care or defence.

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It also seems logical that signals within an organism are responsible for the regulation of metabolism or organ function, as is the case with hormones. This is one of the branches of chemical life sciences which has been investigated most intensively and which holds the most promise for the future.

2. Chemotaxis in Plants

It was not necessarily expected that such communication sequences of stimuli and information would be found in plants which were rooted to one spot. However, observations made over a century ago show that, at least as far as lower plants are concerned, communication between individuals occurs by means of chemical compounds[4]. This is not surprising since chemotactic processes and even motile gametes are found in the generation cycle of these thallophytes. The broad spectrum of such signal substances is illustrated by some examples taken from fungi: mucorales with their trisporic acid system, *Achlya* with their antheridol/oogoniol cycle and *Allomyces* with sirenin have all developed chains of communication which aid in the formation and location of a sexual partner. These substances are all terpenoids, the *Achlya* compounds are even steroids; there is thus an interesting similarity between them and mammalian sex hormones[5].

Brown algae or seaweeds (Fig. 1) are widely distributed throughout the oceans and continental shelf regions of the world. They are technically important firstly as sources of polysaccharides (alginic acid, agar-agar *etc.*), and secondly as food for human consumption, as anyone who has travelled to Japan will know. The oily contents of the Pacific seaweed (*Dictyopteris*, see Table 1) was used in ancient times as a substitute for mustard in Hawaii[6]. Their most interesting features from the biologist's point of view are the diverse forms and different ways which nature has adopted to maintain and distribute this type of marine flora. In addition to simple vegetative cycles where sporophytes form zoospores, there are also several types of sexual reproduction, although the importance of this varies as far as the survival cycle is concerned. As is the case in higher animals some forms must regularly undergo an alternation of haploid and diploid phases; in the case of other species generative reproduction merely increases their chance of surviving and adapting under stress conditions. In all cases, however, sexual plants or gametophytes are formed which produce the (motile) sex cells. These sex cells are of opposite polarity. If they cannot be distinguished from one another morphologically they are called plus and minus gametes—isogamy; if the two types of sex cells are motile but of different sizes they are referred to as gyno- and androgametes—anisogamy (the larger ones are generously designated as the gynogametes and the smaller ones as the androgametes); finally there is oogamy in which large immotile egg cells and many small spermatozoids are formed. The latter situation is regarded as being the most highly developed and it is here, namely in *Fucus serratus* and in the closely related *Fucus vesiculosus*, that it was first suspected that the male sex cells were directed to the female

Fig. 1. "Portraits" of some brown algae. a) *Desmaresta aculeata*, b) *Cutleria multifida* (both ca. 30% natural size), c) *Fucus serratus*, d) *Laminaria digitata* (both ca. 15% natural size) (Photograph: Prof. D. G. Müller, Universität Konstanz).

eggs by a diffusible signal[7]. This was confirmed approximately a century later[8].

2.1. Laboratory Culture and Pheromone Isolation

It is difficult to work with the often very large species of algae which are found in the ocean. Species such as the giant kelp (*Macrocystis pyrifera*), which may reach a length of 60 m, or the *Laminaria* species found in our coastal waters which measure up to 5 m, or even the meter long *Fucus* are only suitable for field studies and marine stations. It is easier for "landlubbers" to work with Mediterranean spe-

cies which are more suitable for the laboratory scale: examples are *Ectocarpus siliculosus* or *Cutleria multifida*, which is distinguished by a remarkable alternation of generations; fusion of one of its gynogametes with an androgamete produces a zygote which develops into a small motile crust-like precursor *(Aglaozonia);* this later forms spores which grow into the seaweed which is about as long as an outstretched hand. It is here that the gametangia are formed.

The alga *Ectocarpus siliculosus* has become a popular, easy-to-handle research tool in connection with (unconfirmed) hypotheses on "relative sexuality"[9]. This alga has been employed for the detailed study of the seasonal rhythm of sexual events and their dependence on external parameters[10]. Gametangia are produced mainly when environmental conditions deteriorate; gamete release depends on the time of day but can also be induced by changes in temperature. *Ectocarpus* is a dioecious isogamic form with physiological anisogamy. Petri dishes containing mature (+)-(gyno)gametes release a fine, aromatic scent when opened; this is not observed with male (−)-cultures. The scented compound is lipophilic, soluble in organic solvents, condenses at low temperatures, can be adsorbed on charcoal, and desorbed by heating, *i.e.* it is stable and of low molecular weight. If vaseline or oil droplets are allowed to absorb some of the scented compound from the atmosphere above ripe gynogamete suspensions and are then presented to androgametes in suspension, the latter will accumulate around this lure. This phenomenon provides the basis for a biological test which is used for monitoring purposes when isolating the attractant. The properties of the scented substance are such that simple or refined gas chromatography is the ideal method for its purification, whereas nuclear magnetic resonance and mass spectrometry are used to determine the structure of the isolated compounds and their hydrogenation products. The methods for collecting and processing volatile active substances released into the surrounding sea water by brown algae gametes have been continually refined and improved during the course of the investigations which have now been going on for approximately ten years. The original methods of distilling off and freezing out[11] have been replaced by adsorption onto activated charcoal in a closed loop, as described by *Grob* and *Zürcher*[12], and modified to near perfection by *Gassmann*[13] for the problems in question. The procedure had to be scaled down because of the very small quantities of volatile substance involved[*]. Air bubbled through a gamete suspension is circulated through a charcoal filter which is extracted occasionally with dichloromethane. The substances collected are then analyzed by combined GC/MS.

The processing of the active substance from *Desmarestia* will be described as an example[15]. This brown alga forms large vegetative plants and small gametophytes which only consist of a few cells; the female gametes found in their gametangia liberate a bouquet of three substances (**1**—**3**). Desmarestene **1** serves not only as an attractant but also instantaneously releases the spermatazoid from the gametangium by an as yet unknown mechanism, but probably by activating an enzyme which lyses the gametangium's capsule. The substances released by the *Laminaria*[14] and *Chorda tomentosa* gynogametes[16] have an analogous action. The two other substances viridiene **3** and ectocarpene **2** are species and genus specific, respectively, but do not display any known biological activity here. If the isolation is to be successful, the gametes should be used exactly when pheromone is produced. Mature female gametes of *Desmarestia* give a chromatographic profile (B) showing the significant peaks of the three C_{11}-hydrocarbons, which, however, do not appear in the profile of immature gametes (A)[15] (Fig. 2).

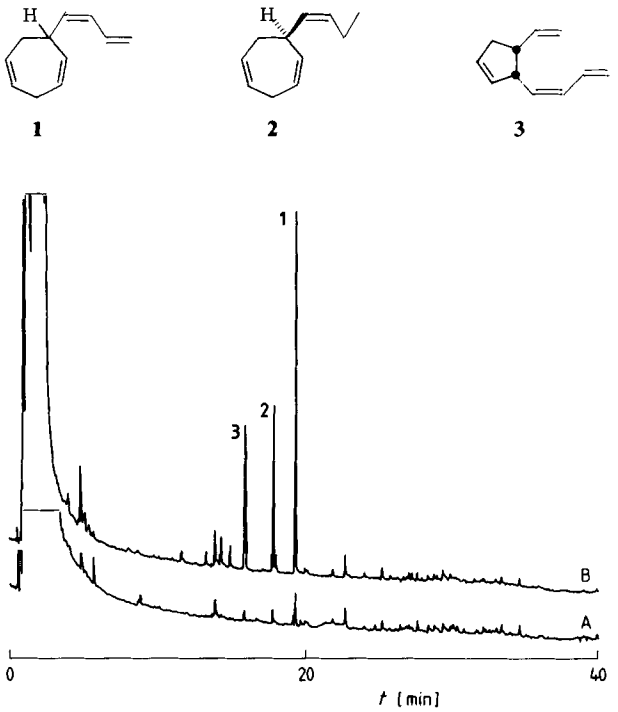


Fig. 2. Capillary gas chromatography of *Desmarestia viridis* gametophytes. Significant pheromone production is only detected after liberation of the gynogametes (B). Prior to this, blank runs (A) show an indifferent pattern with no recognizable major products. All structures were confirmed by synthesis [32], co-chromatography with the authentic substances, and quantitative bioassay [15].

"Sirenins" have been isolated with the help of these methods from eight species of brown algae which all exhibit different stages of evolutionary development; the constitution of these compounds has also been elucidated. The structures were mainly deduced from only a few parameters but were all confirmed by synthesis. When possible the syntheses were designed so that homologs and analogs could be prepared.

2.2. Algae Species and their Signal Substances

Mature gynogametes of *Ectocarpus* from more than 1000 culture dishes were collected by means of their phototaxis; 7 mg of the pheromone was obtained from this suspension by the evaporation procedure. On the basis of mass and NMR spectroscopic data the structure of ectocarpene **2** was established to be 6-(1*Z*-butenyl)-1,4-cycloheptadiene,

[*] Some idea of the scale involved is given by the following figures: In one minute a gynogamete of *Laminaria* produces 10000 molecules of the specific hormone, 15000 molecules of ectocarpene, and 30000 molecules of *n*-pentadecane [14].

$C_{11}H_{16}$[17]. This natural product is dextrarotatory ($[\alpha]_{578}^{22.5°}$ 82°); diimide reduction of the side chain and ozonolysis of the resulting 6-butyl-1,4-cycloheptadiene give (*R*)-2-butylsuccinic acid which shows that ectocarpene is (*S*)-(+)-6-(1*Z*-butenyl)-1,4-cycloheptadiene.

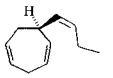
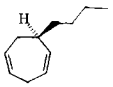
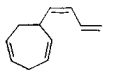
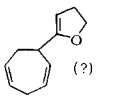
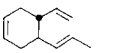
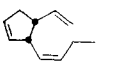
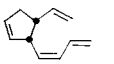
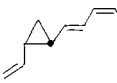
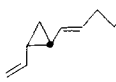
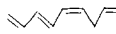
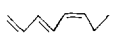
Ectocarpene is also the major product of the dioecious marine alga *Sphacelaria furcigera*[16], whereas in other iso- and anisogamic forms of the Phaeophycidae[*] it occurs as a secondary component of the total bouquet. It may in this case be an evolutionary relict, serve as a chemotaxonomic leitmotiv or, in individual cases where the same habitat is shared, may be used for chemical defence of the surroundings and to ward off competing neighbors. This theory would seem to be justified if anisogamic forms are present which naturally produce mature fertilizable females only in small numbers. Although in this case the zygotes will possibly be better equipped for survival, their gynogametes have a poorer chance of being encountered by males. If the chances of the isogamic forms—approximately equal numbers of plus and minus gametes—are reduced by luring some of the minus gametes away, the chances of the higher form will be accordingly greater. This mimicry is only advantageous for forms which live in the same surroundings; however, it stands on somewhat shaky ground in so far as primitive species are by no means dependent on sexual reproduction with zygote formation; they only resort to this mechanism if the environmental conditions deteriorate.

Ectocarpus is one of the less evolved isogamic forms. *Cutleria multifida* is anisogamic, whereas the closely related *Laminariales* are oogamic. *Dictyota* is characterized by unicellular oogonia but the antheridia are still multicellular; the oogonia and antheridia of *Laminaria* each only contain one gamete. Pheromone mixtures derived from C_{11}-hydrocarbons have been detected in all these Phaeophycidae (cf. Table 1). In *Cutleria* the mixture consists of ectocarpene **2** (5%), aucantene **6** (27%), which does not attract gametes, and the biologically active compound multifidene **7** (68%)[19]. Multifidene (85%) is also found in *Chorda tomentosa* extracts along with ectocarpene (8%), 6-butyl-1,4-cycloheptadiene **4**, and two other products (5%); the combination of all these compounds is responsible for the final bouquet[16]. **4** is also the major product of *Dictyota* eggs and at higher concentrations causes massive attraction of the corresponding androgametes[20]. More highly unsaturated derivatives of the C_{11}-polyenes mentioned are found in the gynogametes of the genus *Desmarestia aculeata* and *Desmarestia viridis* (cf. Fig. 2): the biologically active substance desmarestene **1** (60%) and the hydrocarbon viridiene **3** (20%); ectocarpene **2** (20%) is also present as is usually the case in this subclass[15].

In *Laminaria digitata* and *L. hyperborea* an ectocarpene derivative with an oxygen group in its side chain has been identified; this compound is presumably derived from desmarestene and serves both for release and attraction of the androgametes[14]. Its structure is still unknown, however, as only minute quantities can be produced and isolated in the laboratory. The suggested formula **5** is plausible and is based on synthetic evidence[16].

Moore[21] has isolated several "dictyopterenes" not as sexual pheromones but from vegetative parts of the Pacific seaweeds *Dictyopteris australis* and *Dictyopteris plagiogramma*; these compounds were shown to be C_{11}-hydrocarbons. Dictyopterene B **8** was found and can readily be thermally or photochemically converted into ectocarpene **2** (chair form, diradical transition state)[22]. Dictyopterene A **9**, which is isomeric with **4**, was also identified (cf. Section 4). In addition, *Dictyopteris* contains 1,3*E*,5*Z*,8*Z*-undecatetraene **10**, an open chain isomer of dictyopterene B **8**, aucantene **6**, multifidene **7** and ectocarpene **2**. The hydrocarbon **10** is also the sex-specific substance of the marine alga *Spermatochnus paradoxus*[23]. Lower molecular

Table 1. Signal substances and other compounds found in brown algae. An asterisk indicates that the substance acts as an effective attractant for the species in question.

Formula		Name	Species
	**2**	Ectocarpene $C_{11}H_{16}$	*Ectocarpus siliculosus** [1], *Sphacelaria furcigera* [16], all *Phaeophycidae* with the exception of *Dictyota dichotoma* [20], *Spermatochnus paradoxus* [23]
	**4**	Dictyopterene C′ $C_{11}H_{18}$	*Dictyota dichotoma** [20], *Dictyopteris australis* and *Dictyopteris plagiogramma* [21]
	**1**	Desmarestene $C_{11}H_{14}$	*Desmarestia aculeata** and *Desmarestia viridis** [15]
	**5**	$C_{11}H_{14}O$	*Laminaria digitata** and *Laminaria hyperborea** [14]
	**6**	Aucantene $C_{11}H_{16}$	*Cutleria multifida* [19]
	**7**	Multifidene $C_{11}H_{16}$	*Cutleria multifida** [19] *Chorda tomentosa* [16]
	**3**	Viridiene $C_{11}H_{14}$	*Desmarestia aculeata* and *Desmarestia viridis** [15]
	**8**	Dictyopterene B $C_{11}H_{16}$	*Dictyopteris australis* and *Dictyopteris plagiogramma* [21]
	**9**	Dictyopterene A $C_{11}H_{18}$ 1,3*E*,5*Z*,8*Z*-	*Dictyopteris australis* and *Dictyopteris plagiogramma* [21] *Spermatochnus paradoxus* [23],
	**10**	Undecatetraene $C_{11}H_{16}$	*Dictyopteris australis* and *Dictyopteris plagiogramma* [21]
	**11**	Fucoserratene C_8H_{12}	*Fucus serratus** [24] and *Fucus vesiculosus** [25]

[*] The class of the brown algae (Phaeophyceae) is divided into two subclasses: (1) The more primitive Phaeophycidae with typical alteration of generations between diploid sporophytes and haploid gemetophytes; it comprises several orders with many species. (2) The more highly evolved Cyclosporidae, pure diplonts, without heterogenesis; it consists only of the orders Fucales and Durvillaeales [18].

weight homologs of **10** serve as attractants which are released from the eggs of the obligatory oogamic *Fucus* species as signal compounds for the 20000 fold smaller spermatozoids. Both *Fucus serratus*[24] and *Fucus vesiculosus*[25] from the North Atlantic give off fucoserratene **11** as their sole active compound. The structure of this substance was established by means of UV, mass, and NMR spectroscopic studies on the signal substance and its hexahydrogenated product (*n*-octane). Synthesis and comparative gas chromatography (Kovàts indices) of all isomeric 1,3,5- and 2,4,6-conjugated octatrienes showed that the natural product **11** was identical with 1,3*E*,5*Z*-octatriene[26].

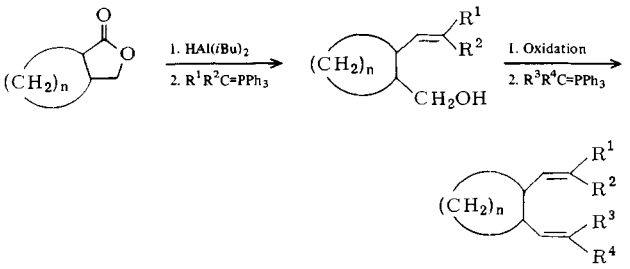
Although the two types of spermatozoid can be attracted to both of the *Fucus* species, these two stable species cannot be cross-fertilized. According to the work of *Bolwell et al.*[27] there must be an immune-type barrier within the surface glycoproteins which ensures species-specific recognition of the egg and spermatozoid.

It should also be mentioned that the analytical patterns of the volatile hydrocarbons of marine algae are generally complex and contain, in addition to the bioactive substances, numerous saturated and unsaturated linear and terpenoid hydrocarbons[28].

3. Pheromone Synthesis

Many pheromones are enantiomerically uniform vicinal dialkylated C_{11}-carbocycles. For their synthesis it is advisable to start with easily accessible, sterically pure *cis*- or *trans*-disubstituted compounds. Bicyclic lactones are most suitable, since they satisfy these requirements and also have two side chain synthons with different oxidation states. Conversion of the synthons into olefinic structures with a defined geometry is a subsequent step of such synthetic sequences.

"Reductive olefination"[29] constitutes a very useful lactone→olefin transformation. The lactones are allowed to react with diisobutylaluminum hydride to give low-temperature stable (−70 °C) organoaluminum substituted hemiacetals (esters react analogously), which then react with phosphoranes at 0 °C to form olefinic alcohols. The second side chain can then be completed with the customary repertoire of reactions (oxidation, Wittig reaction) (Scheme 1). However, if the side chain is first derivatized



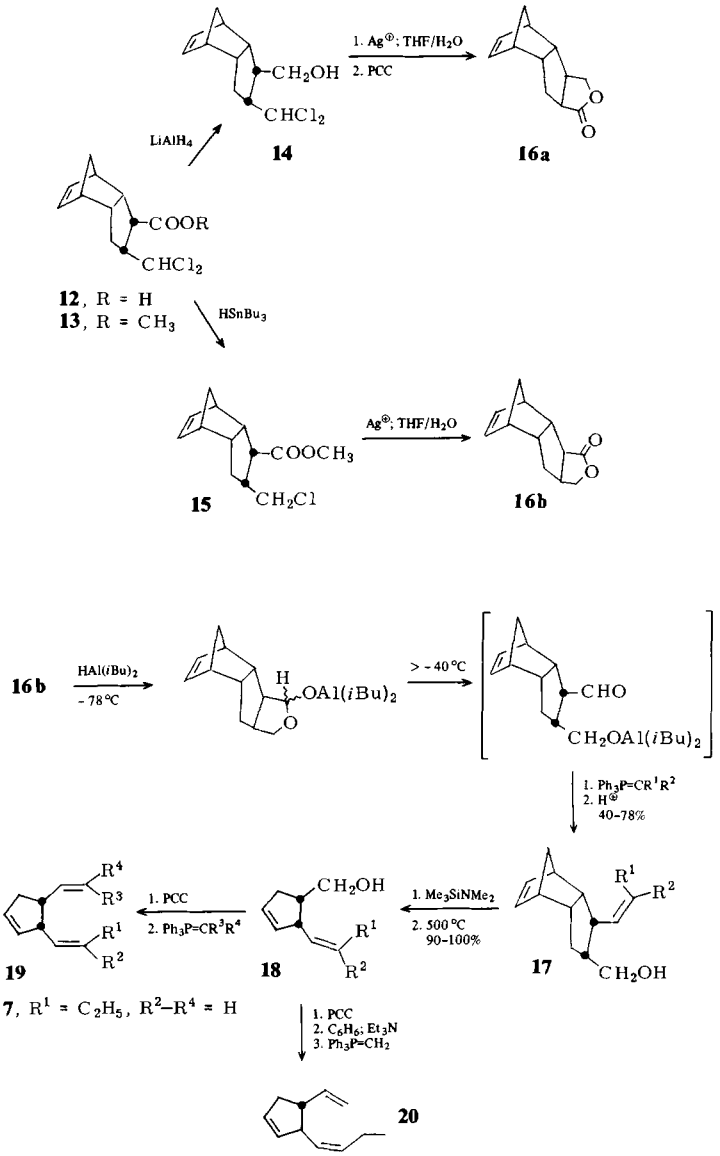
Scheme 1. Principle of the synthesis of brown algae pheromones of types **3** and **6**–**9**.

with optically active reagents, chromatographic resolution can be introduced under favorable conditions; *both* enantiomeric attractant molecules are then accessible. This principle can be applied to all carbocyclic pheromones isolated so far, and will be illustrated using the synthesis of multifidene **7** (Section 3.1).

3.1. Synthesis of Multifidene[31]

Bearing in mind the ultimate aim of performing a wide range of receptor studies, the synthesis of multifidene **7** (Scheme 2) makes special demands as regards stereospecificity and stereoselectivity and the range of possible variations. The synthesis has to take into account the need to alter chain length and chain branching, and ensure uniform geometry and chirality. Heteroatoms also should be introduced without fundamentally changing the basic concept of the synthesis[30–33].

The α-(dichloromethyl)carboxylic acid **12** proved to be a highly suitable starting compound, which can be synthesized in a few steps in high yield from dicyclopentadiene and dichloroketene[34]. After esterification of **12** with $BF_3 \cdot MeOH$ to **13**, reduction of one of the two side chains determines the stereochemistry of the lactone **16a** or **16b**. Selective dehalogenation of **13** with tri-*n*-butyltin hydride

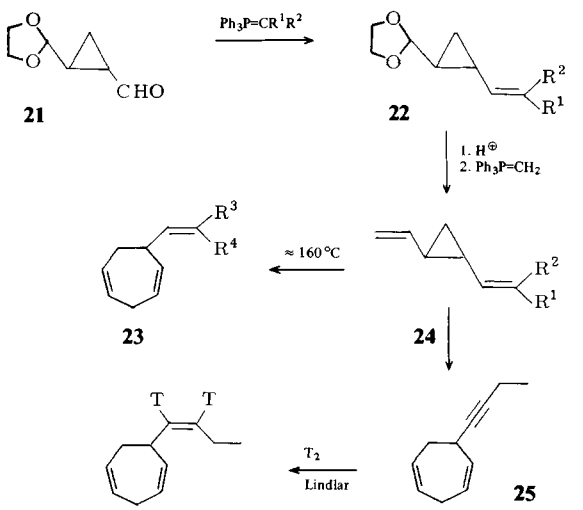


Scheme 2. Synthesis of multifidene **7**. THF = tetrahydrofuran, PCC = pyridinium chlorochromate.

produces the monochloro ester **15** and subsequent cyclization yields the key compound **16b**. Side chains with various residues (R^1; R^2) can be introduced smoothly into **16a** or **16b** with uniform stereochemistry by "reductive olefination"[29], to yield olefinic alcohols of type **17**. The cyclopentadienyl protecting group is readily removed by flash pyrolysis without altering the existing geometry; the monomeric alcohols **18** are then formed as versatile intermediates, which can be modified in a number of ways. After oxidation to an aldehyde, the second side chain (R^3; R^4) in **19** can be modified by employing the entire range of Wittig reactions. Reaction of **18** with optically active phenylethyl isocyanate yields diastereomeric carbamates which can be resolved into their enantiomers by simple chromatography on silica gel[35] (>97% e.e.). The chiral attractants can be obtained from these compounds in a high degree of optical purity in a few steps. *trans*-Disubstituted "multifidenes" **20** can be prepared after base-induced rearrangement of the intermediary aldehyde, thus completing the synthesis in this direction. Heteroatoms (*e.g.* a homologous series of halogens) can also be easily introduced into the alcohols **18** giving an array of molecular "probes", all with the same shape and volume[36].

3.2. Synthesis of Ectocarpenes and Dictyopterenes[37]

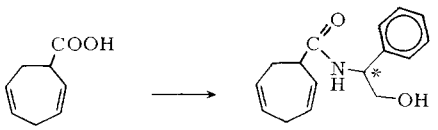
The synthesis of ectocarpenes and dictyopterenes begins with the versatile compound, **21**, the monoacetal of *trans*-cyclopropanedicarbaldehyde, which is allowed to react with various Wittig reagents (R^1; R^2) to give the desired alkenylcyclopropylcarbaldehyde acetal **22** (Scheme 3).



Scheme 3. Synthesis of ectocarpenes (**23**, R^3 = H, R^4 = C_2H_5, = ectocarpene **2**) and dictyopterenes (**24**, R^1 = H, R^2 = Z-$C_2H_5CH{=}CH$, = dictyopterene B **8**; **24**, R^1 = H, R^2 = C_4H_9, = dictyopterene A **9**), schematic.

The basic C_{11}-skeleton is completed by performing a second Wittig reaction—in principle any Wittig reagent may be chosen, but for this present class of natural products methylenephosphoranes are the obvious reactants—only a few steps are then required to synthesize the dictyopterenes (type **24**). Subsequent Cope rearrangement at approximately 160 °C (chair form, diradical transition state) yields ectocarpenes (type **23**), which can also be obtained with various side chains (R^3; R^4) by the same method. Acetylenic cyclopropane derivatives can also withstand the conditions of the Cope rearrangement intact; radiolabeled ectocarpene can thus easily be obtained by tritiation of butynylcycloheptadiene **25**[38].

The brucine or strychnine salts of 2,5-cycloheptadiene-1-carboxylic acid **26** are not very suitable for the synthesis of optically active ectocarpenes (<30% e.e.)[39]; a method was therefore chosen which is analogous to the liquid chromatographic separation of diastereomeric γ-hydroxycarboxylic acid amides[40] (Scheme 4).



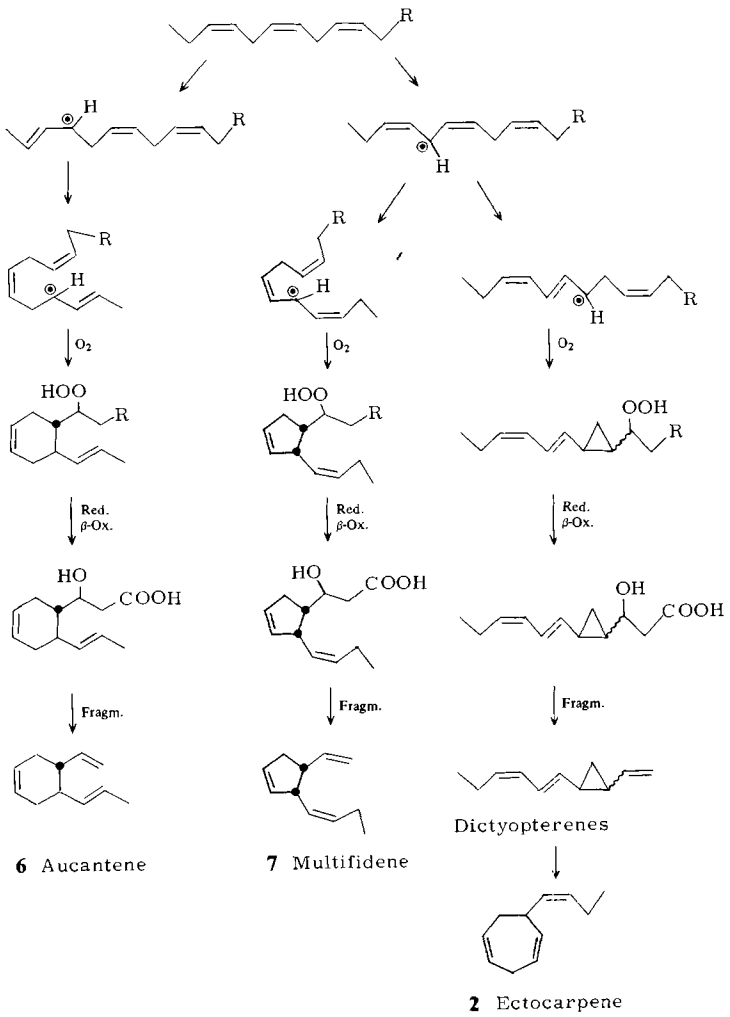
26 **27**

Scheme 4. Preparation of the diastereomic amides **27** from the acid **26** with 1) *N,N'*-carbonyldiimidazole and 2) 2-amino-2-phenylethanol.

26[37] is converted by reaction with *N,N'*-carbonyldiimidazole into the reactive imidazolide, which is allowed to react with optically pure 2-amino-2-phenylethanol ("phenylglycinol") to give the diastereomeric pair **27**: this can be resolved into its two enantiomers on silica gel columns (Nucleosil 50-5) with a factor $\alpha = 1.2$[41]. *Kajiwara et al.*[42] used a biochemical method; they diastereoselectively saponified ethyl 2,5-cycloheptadiene-1-carboxylate with *Rhodotorula* species. The resulting optical yields were 78 and 95% e.e.; these authors were also able to resolve the diastereomeric quinine salts (95% e.e.).

4. Biogenetic Relationship of C_{11}-Hydrocarbons

It is obvious that there is a structural similarity between the sex-specific pheromones of brown algae species so far isolated (compiled in Table 1). They all contain a vinyl or cycloheptadienyl group and, depending on their origin, a *Z*-butenyl, *E*-propenyl or *E*-hexenyl group (in some cases these groups are hydrogenated or dehydrogenated). Some also exhibit a homoconjugated 1,4-rhythm, which is characteristic of polyunsaturated fatty acids. We have further seen that the C_{11}-polyenes may also have rings of varying sizes; cyclopropane, cyclopentene, cyclohexene, and 1,4-cycloheptadiene are found. In the C_8-compounds the ring structure is absent, but vinyl and *Z*-butenyl terminal groups are present. Fatty acids are more obviously the biogenetic source of 1,3*E*,5*Z*,8*Z*-undecatetraene, in which the aliphatic fatty acid terminus is almost unchanged. This comparison suggests that the pheromones are biogenetically related to one another, whereby linolenic acid may be a common precursor. This compound occurs not only in marine algae (from where it reaches the liver oil of fish) but also has a terminal *Z*-butenyl group. Lower molecular weight homologs may also be suitable starting compounds *e.g.* dodecatrienoic acid, which can be produced from linolenic acid by three consecutive β-oxidations. It seems plausible that these natural products may be formed in the membrane fractions of gynogametes from (β-oxidized) polyenic fatty acids by a combination of radical cyclization and subsequent heterolytic fragmentation.



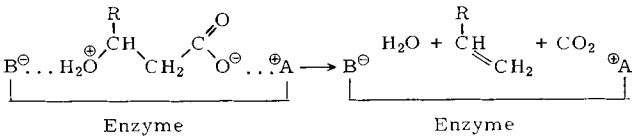
Scheme 5. Model for the biogenesis of C_{11}-polyenes from unsaturated fatty acids. Red. = reduction of hydroperoxides, β-Ox. = β-oxidation, Fr. = heterolytic fragmentation.

The reaction sequence postulated in Scheme 5 is based on the following considerations:

- One of the olefin-flanked CH_2 groups is activated as a radical by analogy to the primary step of lipoxygenase-catalyzed reactions. In radicals the entire flexibility of the lipid chain is retained, which is not the case in cationic structures.
- The reactive species can undergo cyclization either directly (multifidene) or after rearrangement (dictyopterenes) to give a conjugated pentadienyl radical. Positioning at the active center of the enzyme concerned largely determines the ring size and substitution pattern (note the analogy between conjugated C_{11}-hydrocarbons—*E,Z* geometry— and the products of lipoxygenase reactions).
- After ring closure or rearrangement, reaction with oxygen (ground state) terminates the radical process yielding hydroperoxy acids (Δ^9) if the starting molecule is linolenic acid, Δ^3 if it is dodecatrienoic acid).

Reduction of the hydroperoxides and triple β-oxidation (only in the case of linolenic acid) leads to the formation of 3-hydroxy acids. These compounds act as substrates for heterolytic fragmentation in which the functional groups present are removed in the form of CO_2 or H_2O.

The mechanism of this fragmentation involves general acid/base catalysis (Scheme 6).



Scheme 6. Fragmentation by general acid/base catalysis.

Longer chain or more highly unsaturated fatty acids are also possible educts for this reaction, for example arachidonic acid which could be liberated from membrane phospholipids by a phospholipase.

Similar lipid-activating, oxygen-dependent enzymes may be involved in the genesis of C_8-compounds (*e.g.* fucoserratene **8**). A diol intermediate could thus be obtained from 1,5*Z*,8*Z*-undecatrien-3-ol, and *Yamada et al.* established that this compound is present in *Dictyopteris* species[43]. Fragmentation of the diol intermediate with retention of the 5*Z*-geometry would then produce fucoserratene **8**. Retention of the 5*Z*-geometry has been confirmed experimentally by means of biomimetic model reactions[44].

A South African composite *(Senecio isatideus)* has proved to be of value for such biogenetic experiments; when in flower this species contains considerable quantities of ectocarpene in its aerial parts[45], whereas sesquiterpenes and a range of open chain C_{15}—C_{17}-hydrocarbons are to be found in the roots[46]. The latter compounds all possess a characteristic vinyl group and double bonds at the positions expected if they are derived from polyunsaturated fatty acids. Biogenetic experiments with labeled precursors have been performed with both *Senecio* and dyer's thistle *Carthamus tinctorius*, whose seedlings also contain significant quantities of vinyl hydrocarbons in their lipids shortly after germination[47]. 1-Pentadecene, 1,8*Z*,11*Z*-heptadecatriene, and 1,8*Z*,11*Z*,14*Z*-heptadecatetraene (major product) have been identified in the very early developmental stages (this profile is comparable with that of *Senecio*). Labeling experiments with ^{3}H-linolenic acid were therefore first carried out on this easily accessible plant. Incorporation ratios of up to 4‰ were found, which support the hypothesis that these fatty acids act as precursors[48]; it is open to discussion whether activated derivatives of the fatty acids take part in these reactions.

5. Reception of Signal Substances

It is still not known exactly where the attractant is bound to the androgametes, how its stimulus is processed and transmitted to the motile flagella and, finally, how the signal is terminated and inactivated. Preliminary experiments with labeled ectocarpene **2** suggest that the receptors are grouped around the attachment sites of the flagella. By analogy with observations on chemotactic microorganisms it can be concluded that the transmission and processing of the stimulus involve the chemical or conformational modification of binding, carrier, adaptation, and

transformation proteins resulting in a modulation of flagella movement—whether it be by ion or energy flux[49]. Cinematographic studies on the movement patterns of *Ectocarpus*' androgametes indicate that the attractant-sensory system acts on the steering movements of the small flagellum[50]. The dorsiventral gametes react strongly thigmotactically and are pulled along the underlying surface by the large, motile flagellum which is equipped with passively moving side hairs (mastigonemata). The gametes do not, therefore, swim freely but rather crawl in the limited space between seaweed filaments or along the surface of a brown alga thallus or some other surface. The gametes initially move in a straight line or wide circle but this is changed in presence of a lure to a right-handed spiral by an increase in the beating frequency of the short flagella. The males thus first encircle and finally reach the source of the attractant, the gynogamete, if positioned to the right (Fig. 3). An emitter to the left is missed and the gamete, after passing through the signal gradient, resumes its straight movement without hitting the goal. Thus, net mating probability is 0.5.

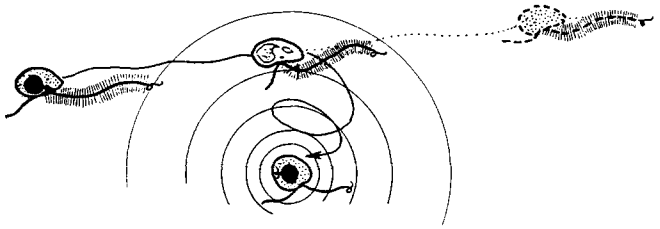


Fig. 3. Changes in the movement patterns of algae gametes in an attractant gradient. An increase in the pheromone concentration increases the beating frequency of the asymmetrically arranged short flagella, this causes the gametes to move in a right-handed spiral and reach the gynogametes.

The sender (emitter) can be located due to the fact that one or all of the conformatively altered proteins have a memory (which must be short-lived so that a gradient can be detected and followed). The spatial data can be transformed into time-based information by inactivation of the stimulant, so that the system only requires one type of receptor and can dispense with a gradient control along the gamete (dc/dx). The still largely hypothetical model of stimulus response in unicellular eukaryotic organisms requires specific receptors; we have, however, shown the existence and action of these receptors by chemical and sensory physiological experiments.

5.1. Biological Activity Assay

We have utilized a modification of the method mentioned in Section 2.1 to obtain quantitative data about the informational value of an attractant[51]. Microdroplets (0.1 μL) of serial dilutions of the attractant in a biologically inert perfluoro ether (FC 78)[*] are brought into contact with gamete suspensions for a defined length of time in the dark (to eliminate phototactic interference). A solvent blank is also determined. A flash-light dark-field exposure is made and the number of gametes found in a given area is compared with a corresponding blank[**]. The value obtained is reproducibly proportional to the concentration of the attractant, so that a dose-response curve can be drawn. If the results are plotted logarithmically, the curve almost becomes a straight line, indicating that the Weber-Fechner law also applies to these primitive sensory cells (logarithmic dependence of stimulus strength and stimulus response). The stimulus threshold is the limiting concentration at which the sample value just exceeds the blank. The actual concentration of the active substance (C_L') is obtained by employing the appropriate distribution coefficients (K_{fcw}) of a substance between the organic phase (FC 78) and seawater. The distribution coefficients are determined by gas chromatography or UV measurements (in the case of conjugated compounds). The product of the threshold concentration in the organic phase (C_L) and K_{fcw} corresponds to the actual concentration of the active substance in the aqueous phase (C_L')[52].

Under the stringent conditions assumed, experimentally reproducible results are obtained, which can be rationalized and open up systematic investigation of the signal substance/binding site system. Quantitative evaluation gives impressively low values for the threshold concentrations of pheromone in the aqueous phase which are necessary to trigger off a stimulus. In the (*S*)-(+)-ectocarpene/*Ectocarpus* and (+)-multifidene/*Cutleria* androgamete systems the values were determined to be 8.9×10^{-10} mol/L[54] and 6.5×10^{-12} mol/L[52], respectively. After consideration of the swimming behavior, reaction time, and the action volume of the gametes it has been calculated that 1 to 10 attractant molecules are required per gamete to effectively trigger the luring reaction. Comparison of the steepness of the stimulus/response curves and the thresholds for stimulation in the systems is of illustrative value. The gametes of the primitive, isogamic *Ectocarpus* have low sensitivity and do not need to travel long distances within the closely woven environment of filamentous gametophytes. A strongly attracting sign language is not called for as there are equal numbers of andro- and gynogametes, whereas in anisogamic and oogamic forms more effective systems of communication had to be developed. The steepness of the response curves of the multifidene/*Cutleria* androgamete and fucoserratene/*Fucus* spermatozoid receptor systems are accordingly much greater[51]. As is the case in all the other systems a range of approximately 1 mm is sufficient for the biotope (Fig. 4).

The specificity of the attractant systems is also quite remarkable. In the natural system only the attractant of the species in question is highly effective; however, it can pro-

[*] FC 78 is a trade name of the 3M Company for a low molecular weight perfluoro ether with the empirical formula $C_8F_{16}O$.

[**] The result is expressed as an attraction ratio Q = number of gametes per standard area of the sample divided by the number of gametes per standard area without attractant, and is then treated statistically. By definition, the uncorrected threshold concentration of a substance is attained when Q tends to a value of 1.00. This activity test is based on a knowledge of the limiting concentration in the aqueous phase surrounding the gametes directly above the FC 78 limiting surface. The diffusion rates of the signal substances must therefore be taken into consideration. According to Fick's first law the number of molecules transported in a given time is given by $dn/dt = -AD \cdot dc/dt$ and is thus related to the concentration in the FC 78 phase. The population above the sample droplet is therefore time and concentration dependent. The influence of these effects was determined by counting the number of gametes above the droplet at 1 min intervals with different concentrations of attractant; the optimal time was found to be 4 min [53]. Furthermore, the prerequisites are that the lipophilic substances must undergo *molecular* dissolution (no micelle formation) and must be chemically stable throughout the measurement.

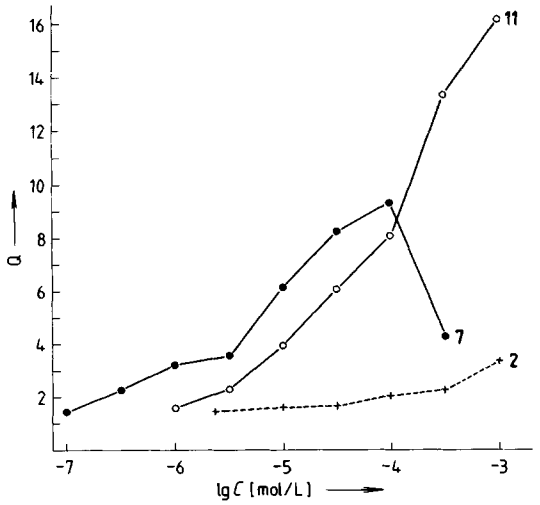


Fig. 4. Dose/response diagram for brown algae attractants (illustration of the Weber-Fechner law). 2 = ectocarpene in *Ectocarpus*; 7 = (+)-multifidene in *Cutleria*; 11 = fucoserratene in *Fucus*. The "luring quotients" Q are plotted against the logarithm of the pheromone concentration C in the organic phase ($Q = K \lg C$).

duce an effect in related forms, although the threshold for attraction is often higher (by several orders of magnitude). *Cutleria* androgametes thus respond not only to multifidene **7** but also to ectocarpene **2**[54]. Scheme 7 offers an explanation for this phenomenon: certain conformations of the two substances resemble each other, hence each substance can bind not only to its "own" receptor but also to the surface of the receptor whose configuration is primarily adapted to fit the other attractant.

Scheme 7.

If the ectocarpene is modified, however, only the *Ectocarpus* system reacts in a sensitive manner; the *Cutleria* system does not exhibit such a behavior. If, for example, the *Z*-butenyl side chain of **2** is substituted by an *E*-propenyl side chain, the informational content for *Ectocarpus* androgametes decreases by a factor of 10^3, but for *Cutleria* spermatozoids only by a factor of ten[54].

5.2. Receptor Scan with Synthetic "Multifidenes"

The multifidene molecule **7** has two side chains and its cyclopentene ring has specific stereochemistry and double bond positions; it is therefore more variable than ectocarpene **2**, and is thus better suited for the investigation of the appropriate receptor. The synthesis described in Scheme 2 was used to prepare more than 40 isomers, homologs, and analogs of multifidene in which the position of the ring double-bond is altered and heteroatoms are introduced into the side chains. The compounds were obtained with a purity of more than 99% by means of preparative gas chromatography[31]. The two enantiomers (+)- and (−)-multifidene were also synthesized in a high degree of purity[35]. The ways in which this molecule may be modified can be classified as follows: 1) The double bonds are reduced or transferred to a different position; 2) One or other of the side chains is shortened or lengthened, with *cis*- or *trans*-orientation; 3) A double bond is substituted by a C-heteroatom group[53].

In the first group the biological activity is generally diminished by a factor of 10^2 if one double bond is absent; loss of further double bonds is less critical (cooperative binding). The activity is also drastically reduced (in extreme cases by a factor of 10^3) in the second group. Only molecules with a *cis* geometry are effective, and this geometry is found in the naturally occurring molecule. Figure 5 demonstrates the differing activities of the enantiomers. The natural (+)-enantiomer is approximately 100 times more effective than its (−)-enantiomer (>98% e.e.). This means that the unnatural enantiomer is almost inactive but, at least, does not have any antagonistic effects.

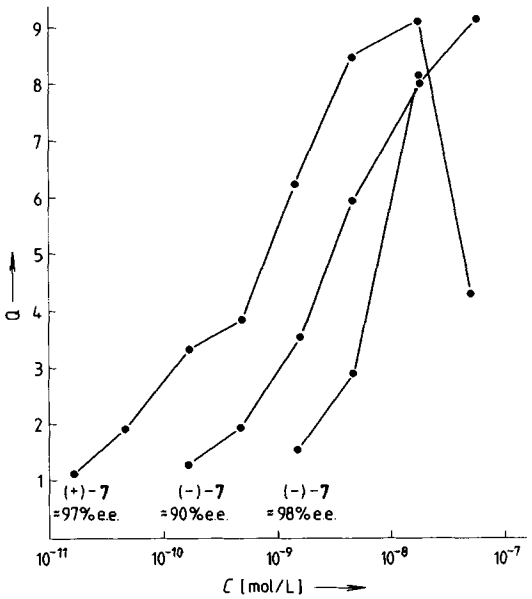


Fig. 5. Dose/response diagram for (+)- and (−)-multifidene **7** (in seawater).

The most important factors controlling binding are, in addition to shape and size, the double bonds in the multiunsaturated hydrocarbon multifidene. Binding to the receptor is thus brought about by π electrons, *i.e.* by induced dispersion interactions. We have proposed a model for the receptor cavity in which dipole/dipole interactions cause the binding of the signal molecule, and where hydrophobic forces play a considerable role in the formation of the ligand/receptor complex at the boundary surface between the water and the gamete surface[52] (Fig. 6).

The specifically constructed receptor surface contains electrophilic groups which are complementary to the double bond positions of the pheromone and therefore cause mutual polarization of the partner. The binding process or a subsequent reaction produces a conformational change in the complex and thus brings about a biological effect. In order to investigate the binding of multifidene to its receptor without disturbing steric, conformational or solvation effects, almost equivalent parapheromones (artificial signal molecules) with systematically modified electronic properties were synthesized[36]. The results of the binding

studies largely confirmed the proposed receptor model and thus gave a clear insight into the primary steps of molecular recognition in the gamete cycle of the Phaeophyceae[53].

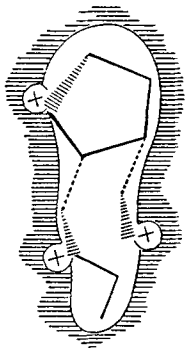


Fig. 6. The "ear" of the gametes for the language of the attraction signals. Schematic representation of the mutual polarization of the ligand (multifidene 7) and receptor. Electrophilic groups whose arrangement is complementary to the π electrons of the signal molecule can contribute to binding and accompanying conformational changes in the receptor/ligand system by induction of dipole moments.

Side chains with strongly polarizable groups play a more important role in determining the activity of the parapheromone than those with more weakly polarizable groups. The biological activity of analogs in which the original vinyl group is replaced by a halomethyl group is greater the stronger the polarizability of the halogen unit. The iodine derivative is, as is to be expected, a perfect imitator of the natural product and even slightly surpasses it (Fig. 7, cf. Scheme 8). The molecules resemble each other both sterically and with respect to their permanent dipole moments (in the case of the latter, resemblance is only approximate) so that the results can be directly related to the electronic properties of the substituent in question. The differences between the dose-response curves of the CH_2Cl and CH_2I derivatives (approximately 1 : 4) is thus a reflection of the higher polarizability of iodine compared with chlorine and the related electron donor properties.

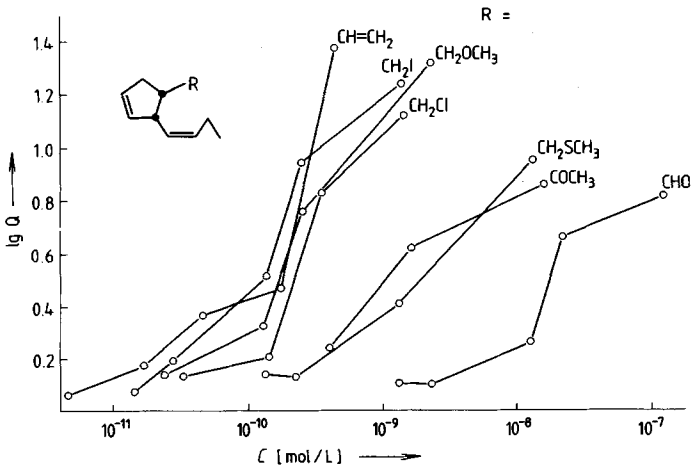
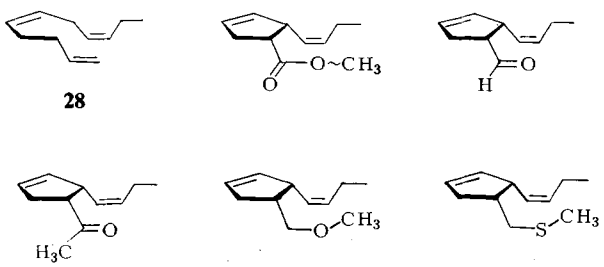


Fig. 7. Dose/response diagram for selected derivatives of multifidene 7 (R = CH=CH_2). All of the curves begin at the actual calculated limiting concentration in the aqueous (seawater) phase (C_L^*).

The oxa- and thiamultifidenes represent another group of parapheromones which are of interest in this context[36,53]. The aldehyde derivative (cf. Fig. 7) exhibits unexpectedly low activity. This can be interpreted as follows: only the bonding electron pair of the C=O double bond is accessible to mutual polarization and formation of a π complex, since it is the only one which is located in the same plane as the electron cloud of the original vinylic double bond. The orbitals of the two lone electron pairs are, however, mutually perpendicular in such a way that they cannot participate in the donor and polarization processes. This accounts not only for the low activity of the aldehyde and the acetyl compound but also for the high activity of the ether. In the ether the polarizable lone electron pair of the oxygen can easily be accomodated in the plane of maximal interaction, since an sp^3-hybridized side chain possesses all the rotational degrees of freedom. This hypothesis is further substantiated by the behavior of the corresponding thioether, which should exhibit typical acceptor properties on account of the vacant 3d orbitals of its sulphur atom. Its biological activity is indeed only approximately 30% of that of the ether, although the two compounds can be regarded as being sterically equivalent (Scheme 8).



Scheme 8. Representation of several mock-pheromones in perspective (cf. Fig. 7).

The ester is of interest, since its activity lies remarkably close to that of the natural substance. The concept of molecular interaction can also be applied successfully here. The electron distribution of the ester can resemble that of the ether, whereby resonance effectively backs-up the polarization effects. Appropriate three dimensional structure and stereochemistry are other important conditions for effective binding of nonpolar molecules. Induced fit does not seem to be solely responsible, since 1,5*Z*,8*Z*-undecatriene **28** can adopt the conformation of multifidene **7**, but is practically inactive. We are, however, aware of the fact that in such a linear molecule the bond lengths do not fully correspond to those of the alicyclic pheromone. The rigid nature of multifidene seems to be necessary to induce the appropriate forces in the receptor.

6. Conclusions and Outlook

The macroscopically observable radius of action of brown algae pheromones barely exceeds 1 mm (depending on the species in question this corresponds to the diameter of 10 to 70 gynogametes), nevertheless these compounds are comparable to the extremely sensitive olfactory systems of insects[55,53]. In the absence of pheromones the androgametes, because of their high speed (up to 350 μm/s), would shoot past their target before their course could be corrected. The pheromones increase the beating frequency

of the small posterior flagellum so that as more pheromone molecules hit their target, and as a result of the pull of the anterior flagellum the androgametes move in a spiral, this spiral movement becomes increasingly narrower and slower. An androgamete which lies outside the "transmitting area" of a gynogamete cannot locate the source of the attractant and will only reach it coincidentally. If this movement can indeed be induced by just a few hormone molecules, we must postulate that there is an effective trigger mechanism in which existing membrane potentials at the surface of the receptor suddenly collapse upon arrival of the chemical signal; this mechanism has also been proposed for the recognition of insect pheromones[56]. This unique sensitivity requires, however, a high signal-to-noise ratio. In the case of the brown algae pheromones this is brought about in the simplest possible way by the largely nonpolar nature of the signal substance in its highly polar aqueous carrier medium. Other mechanisms must dispose of excess pheromone or inactivate it. This is accomplished firstly by the very high volatility of the spherical molecules and secondly by chemical attack at the reactive double bonds *e.g.* the divinyl-methane system in ectocarpene **2**. As has been shown, polar substituents in the attractant molecule result in an almost total loss of activity[52]. This "self cleaning" of the environment can be due to light-induced oxygenation in shallow continental shelf areas, but heavy metal-catalyzed hydration or active enzymatic processes at the surface or inside the gametes may also be responsible.

It can be concluded from our studies, especially those on the multifidene/*Cutleria* system, that the "ear of the gametes" for the language of the attraction signals is located on protein molecules at the cell surface or within the cell. The shape of the "ear" is such that the signal compound fits it exactly and is held tightly at clearly defined positions by maximal interactions resulting from dispersion forces and electrophilic groups. Only the natural (+)-form of multifidene satisfies these requirements and is thus the only substance which can exercise the physiological function of conveying information to the processing units of the gametes. Dipole/dipole interactions with strengths of approximately 13 to 17 kJ/mol are responsible for orientation. Using the threshold concentration of the native multifidene, the total binding energy can be roughly estimated to be 70 kJ/mol. This means that approximately half of the energy is accounted for by forces other than those discussed and measured here. These may well be the entropy terms of the entire attractant/receptor/environment system. We are well aware that the multifidene/*Cutleria* androgamete system only provides a model for the sensory mechanisms involved in smell and taste of higher organisms. The impressive results obtained, however, certainly encourage such extrapolations.

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The Unambiguous Specification of the Steric Course of Asymmetric Syntheses

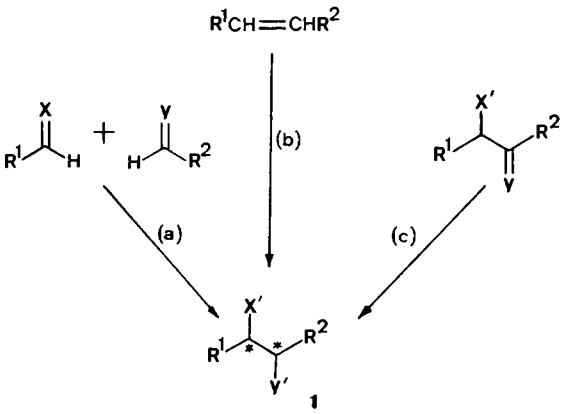
By Dieter Seebach* and Vladimir Prelog

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

The nomenclature of organic chemistry has not kept pace with the staggering advances made in asymmetric syntheses over the last 15 years. Efforts to specify the steric course of stereoselective reactions by use of the terms *erythro* and *threo*, and by other descriptors have led to ambiguous notation and consequently to an almost Babylonic confusion. We propose here a method, based on the CIP-(Cahn-Ingold-Prelog) system, for the unambiguous specification of the steric course and the product configuration of diastereoselective reactions. The reflection-invariant *relative topicity* of approach of reactants is defined as like *(lk)* and unlike *(ul)* if the corresponding descriptor pairs are *Re*,Re** or *R*,Re**, and *Re*,Si** or *R*,Si**, respectively. The descriptor pair notations (*lk* and *ul*) of reactants disclose related steric courses of reactions more often than do the relative configurations of their products, for which the configurational notation $l = R^*,R^*$ and $u = R^*,S^*$ is proposed. The advantage of specifying the relative topicity is demonstrated by means of a series of recent examples of importance to the synthetic organic chemist taken from the literature and from our own work.

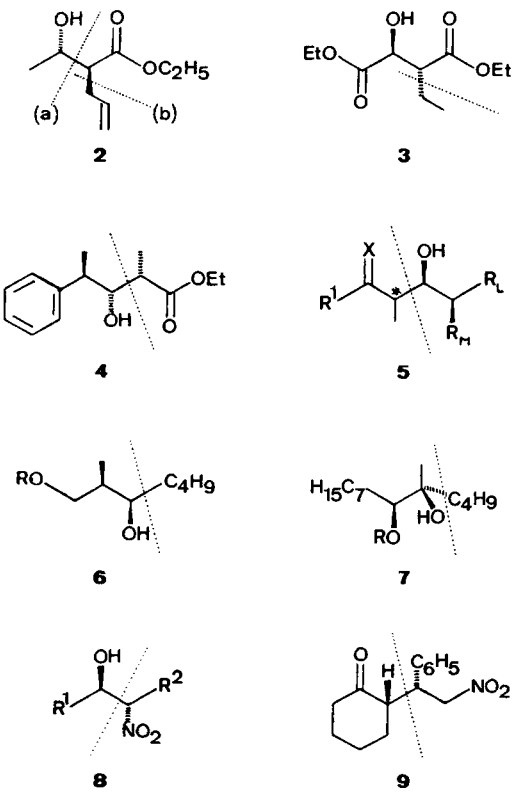
1. Introduction—The Problem

Complex natural products such as macrolides, ionophores, and related compounds have recently become target molecules for synthetic organic chemists[1]. The often formidable array of asymmetric carbon atoms in the structures of these compounds[2] has stimulated the development of highly stereoselective asymmetric syntheses. Foremost amongst these are the aldol[3-5], nitroaldol[6,7], and Michael additions[8]. In all these reactions two planar trigonal carbon atoms are linked together to create a pair of asymmetric tetrahedral carbon atoms [route (a) in Scheme 1]. Stereoselective additions to olefins[9] and to trigonal carbon atoms α to an asymmetric carbon [routes (b) and (c), respectively, in Scheme 1], give the same type of products **1**[7,9-12].



Scheme 1. Three independent routes to structure **1**.

Although these developments represent formidable progress in the art of organic synthesis, attempts to specify the steric course of these reactions have unfortunately led to bizarre nomenclatures, of which the following examples are representative (see Scheme 2): Compound **2** has been termed a "*threo*" aldol product[3,5,17]; **3** an "*erythro*"



Scheme 2. **2a**: *l* by *lk*-aldol addition; **2b**: *l* by *lk*-allylation of an enolate; **3**: *u* by *ul*-ethylation; **4**: *u*, *l* by *ul*-aldol addition with *ul*-1,2-induction; **5**: *lk*-1,2-induction; **6**: *l* by *lk*-addition; **7**: *l* by *lk*-addition; **8**: *u* by *ul*-nitroaldol addition; **9**: *u* by *lk*-Michael addition.

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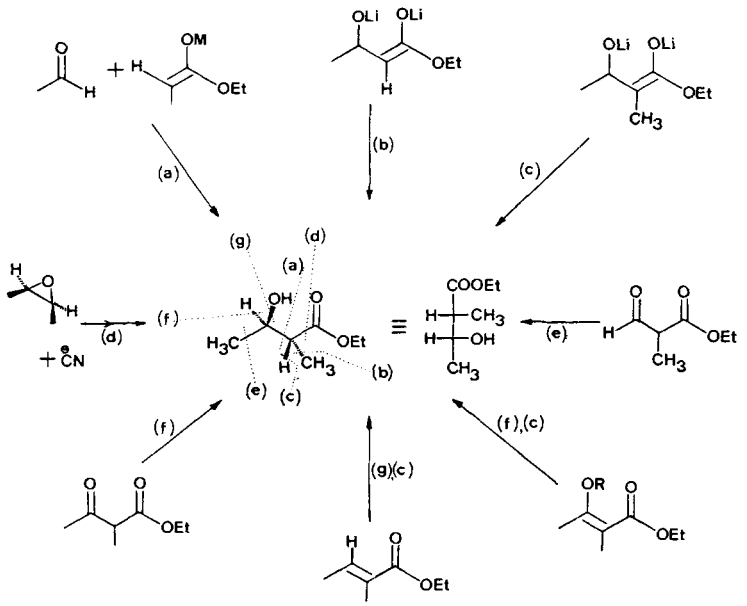
branched malic ester[11]; **4** an "*erythro-anti*-Cram"[3] or "*syn-anti*-Cram" product[4]; **5** a "cram[α- or β-Me]" product, formed in a "CT- (for Cram-*Trans*-enolate) or in a CC (for Cram-*Cis*-enolate)" process[5], respectively; **6** an "*erythro* (Cram steric)" adduct[10a] **7** a "*threo*" glycol derivative[10], **8** an "*erythro*" nitroaldol[7], and **9** an "*erythro*" Michael adduct of an enamine with ω-nitrostyrene[18].

Clearly, there is no agreement about the use of these configurational notations and especially about the meaning of the prefixes *threo* and *erythro*[19]. The attempted redefinition[23] for the purpose of specifying the diastereoselective formation of certain stereoisomers by a particular reaction is certainly not a good basis for configurational notation, because many compounds, such as the β-hydroxyester shown in the center of Scheme 3, can be obtained by



Scheme 3. Formation of *l*-ethyl-3-hydroxy-2-methyl-butanoate with creation of the bonds (a)—(g). (a): *lk*-aldol addition [3–5]; (b): *lk*-methylation of enolate [11, 16]; (c) *ul*-protonation of enolate; (d): opening of *u*-epoxide with inversion (S_N2); (e): *lk*-addition of CH_3-metal derivative [10]; (f) *ul*-hydrogenation of C=O [10b]; (g), (c): *ul*-Michael addition of water to *ul*-olefin; (f), (c): *lk*-hydrogenation of *ul*-enol ether.

several routes [(a—g)], which could well lead to different configurational notations. According to the "aldol-notation"[3,5,17], the (2*R*,3*R*)-3-hydroxy-2-methylbutanoic acid ester in Scheme 3 is specified as "*threo*"; however, according to textbooks of stereochemistry[20] the same compound is specified *erythro*[11].

The present situation in this area is reminiscent of the days when such a simple molecule as dextrorotatory tartaric acid was specified D by European chemists (following *Fischer* and *Freudenberg*) and L by Americans (following *Rosanoff*), because it can be chemically correlated by different reactions with either D- or L-glyceraldehyde[27].

It was in order to avoid such ambiguities that the CIP-system was introduced[28,29]. This specifies the chirality sense of individual two- or three-dimensionally chiral stereogenic atoms (or more generally, stereogenic units, such as centers, axes, planes) by descriptors *Re,Si* or *R,S*, respectively. This system thus specifies not only absolute but also *relative topicities* and configurations by relationships among the descriptors. The duality of diastereomorphic relationships based on combination of two stereogenic atoms and their descriptors leads to two classes which are conventionally specified in the CIP-system (Rule 4[28]) by calling the descriptor pairs with the same first letters (such as *Re,Re*; *R,R etc.*) like (abbreviations *lk* or *l*, respectively) and those with different first letters (such as *Re,Si*; *R,S* etc.) unlike (abbreviations *ul* or *u*, respectively)[28b,30,31].

We now propose an analogous procedure for the unambiguous specification of the steric course of a single diastereoselective asymmetric reaction or of a class of closely related reactions by specifying diastereomorphic relationships between the two-dimensionally stereogenic trigonal atoms and/or three-dimensionally stereogenic tetrahedral atoms in reactants and in products. This will be explained and illustrated by examples.

2. The *Relative Topicity lk* or *ul* of Reactants and the *Relative Configuration l* or *u* of the Products

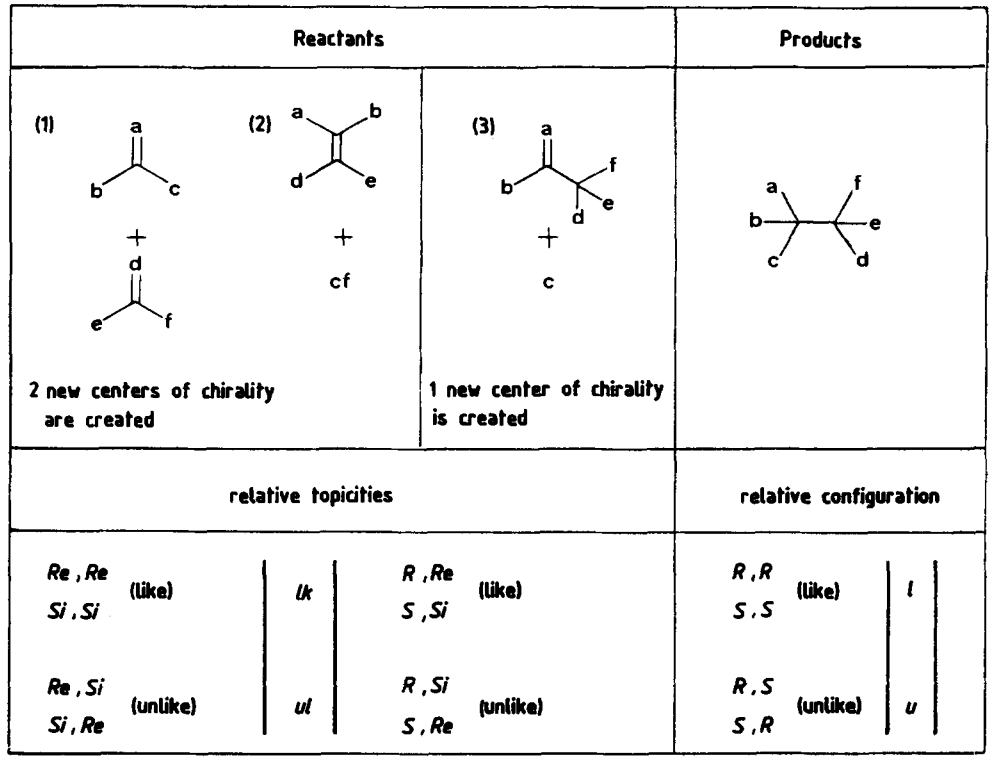
Only one enantiomeric set is shown in all *formulae* representing diastereotopic or diastereomeric relationships. The steric course of reactions leading from reactants with one or two two-dimensionally stereogenic centers to products with two three-dimensionally stereogenic centers is defined by a descriptor pair, and so is the configuration of the product, as shown in Scheme 4. The descriptor pair may be like or unlike. The steric-approach descriptor pairs define *relative topicities*, for instance (*Re,Re*)-approach or addition from the (*Si*)-face of the (*R*)-enantiomer, and are abbreviated as *lk* (like) and as *ul* (unlike), respectively. Similarly, the configurations of the products formed are designated *l* for (*R,R/S,S*) or (*R*,R**) and *u* for (*R,S/S,R*) or (*R*,S**)[30,32]. Procedures for applications to more complex processes or to more complex reactants are given in the legend to Scheme 4.

3. Examples of the Application of the like/unlike Descriptor Pair Notation

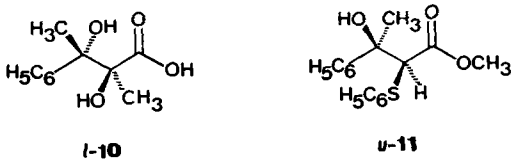
As first examples, the abbreviations *l* and *lk* for like and *u* and *ul* for unlike have been appended for specification of reactions shown in Schemes 2 and 3 (Section 1).

The examples in Scheme 5 show that the *u,l* configurational notation is concise and unambiguous, even in complex cases such as **10**–**12**; in addition, *cis/trans*-diastereomeric olefins, for instance **13** and **14**, can be specified by the same notation[28b].

In Schemes 6–12 a variety of different reactions are specified. Thus, the favored course of aldol and related additions[3–5,8] in nonpolar media turns out to be *ul* with *syn*-enolates and *lk* with *anti*-enolates (see Scheme 6). In Scheme 7 an iodolactonization-type reaction[9], an epoxidation of a homoallylic alcohol[13b], and the conversion of specifically labeled linalol, (*ul,lk*)-1,2,8-trideuterio-3,7-dimethyl-1,6-octadien-3-ol, into terpineol[33] are described with the like, unlike descriptors: the 1,2-induction of the epoxidation in the middle of Scheme 7 is *lk* for all known examples, regardless of the configuration of the atom carrying the hydroxy group[13b]; with the terpineol-forming

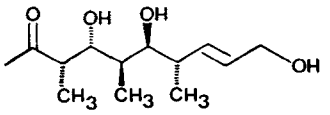


Scheme 4. In complex processes, the relative topicities (1), (2), and (3) are given in this order. The distance between the inducing center of chirality and the reacting atom is specified by 1,2; 1,3; 1,4 ... *etc.* If several centers in the inducing part of the reactant are present, the one which has priority according to the revised CIP system [28] takes precedence.



l-10

u-11



12

13
ul-diastereomer

14
lk-diastereomer

Scheme 5. **12**: (*u,l,u,l,lk*)-4,6,10-trihydroxy-3,5,7-trimethyl-8-decen-2-one; (order of descriptor pairs according to increasing numbering in IUPAC name).

process, the information content of the relative topicity signs is impressive: the *lk*, *ul*, *ul*-1,3 description specifies (a) that the new CC bond is formed with relative topicity *Re,Re/Si,Si*, (b) that the addition of C and O to the C=C bond occurs with *Re,Si/Si,Re* steric approach, and (c) that the (*R*)- or (*S*)-enantiomeric starting material undergoes CC bond formation with *Si,Si* or *Re,Re* relative topicity, respectively.

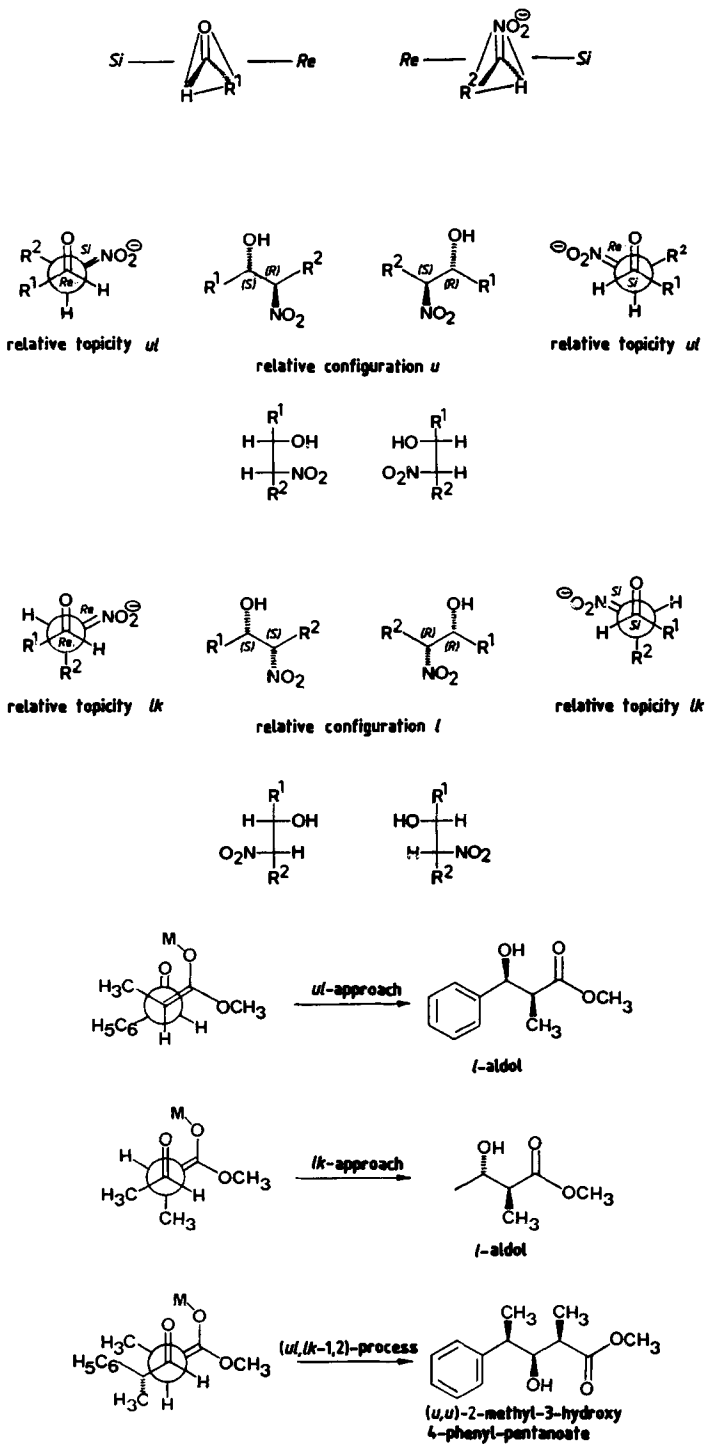
Scheme 8 contains examples of the application of the *lk/ul* descriptor pair abbreviations to reactions following the classical Cram[34], Cornforth[35], and Prelog[36] rules; it is evident, that the acyclic and the cyclic models of the Cram rule are both specified by *lk*. Additions to α-ketoesters of chiral alcohols proceed with *ul*-1,4 induction, irrespective of the priority sequence of the substituents.

In Scheme 9 three examples are shown of reactions which follow a newly established rule for diastereoselective approach of electrophiles to donor double bonds[7, 11, 17].

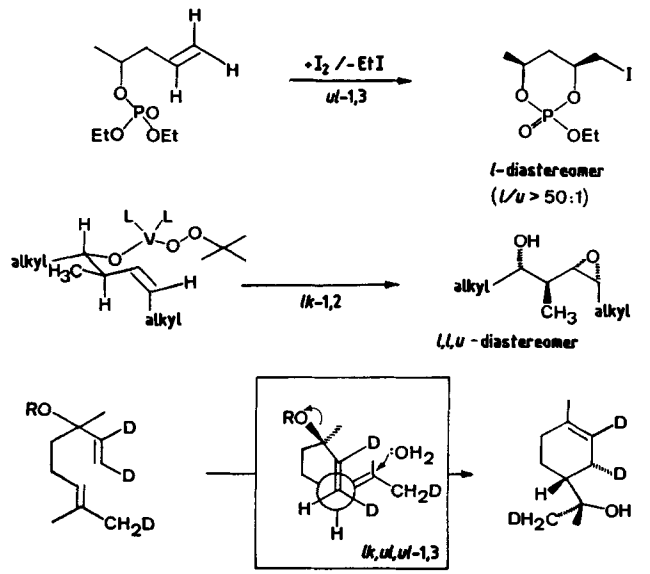
Examples of recently described 1,4- and 1,5-inductions are the reaction sequences (1), (2), and (3) in Scheme 10. The alkylation of the enamine from cyclohexanone and prolinol ether by ω-nitrostyrenes furnishes one of the four possible stereoisomeric 4-nitroketones with >90% selectivity; the first *lk* in the relative topicity specification indicates that the new CC-bond results from a *Re*,Re**-combination of the trigonal centers with formation of the *u*-diastereomer, while the *ul*-1,4 signals that the (*S*)-prolinol ether leads to the (2*S*,1′*R*)-enantiomer of 2-(1′-aryl-2′-nitroethyl)-cyclohexanone[8]. Methylation of the (*S*)-prolinol derivative [see (2) in Scheme 10] occurs from the *Re*-face; a *ul*-1,5 induction[15]. The Michael addition (3) in Scheme 10 can produce[37] (*R*)- or (*S*)-β-branched carboxylic acids, depending upon the sequence in which R^1 and R^2 are attached to the heterocyclic system, with *lk*-1,5 induction.

In Scheme 11, the steric approach in a [2+2]-cycloaddition and in two Diels-Alder reactions is described with the relative topicity notation. Other conversions following the Woodward-Hoffmann rules[38] are of course also amenable to specification by this notation; the intramolecular cycloaddition described in the third equation of Scheme 11 demonstrates the simplicity of the proposed procedure as compared to conventional ways of specification[39].

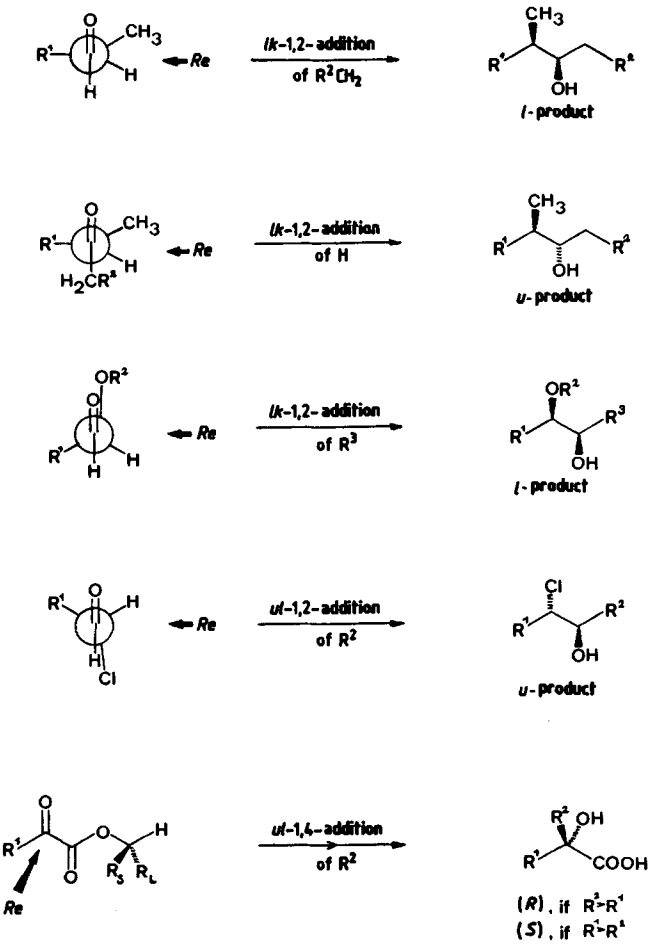
Although not covered by (1), (2), and (3) in Scheme 4, the relative topicities can also be defined in other asym-



Scheme 6. Aldol and nitroaldol additions. Top: Procedure for the specification of the relative topicities of the two possible reactant approaches in the nitroaldol addition and specification of the relative configuration of the products.—Below: Aldol additions of *cis*/*trans*-isomeric enolates to aldehydes. Specification of relative topicities of the first two reactions discloses their different steric course, while specification of the product configurations does not.—The third reaction follows the Cram rule: it exhibits the typical *lk*-relative topicity of the 1,2-induction (see Scheme 8, first three equations).

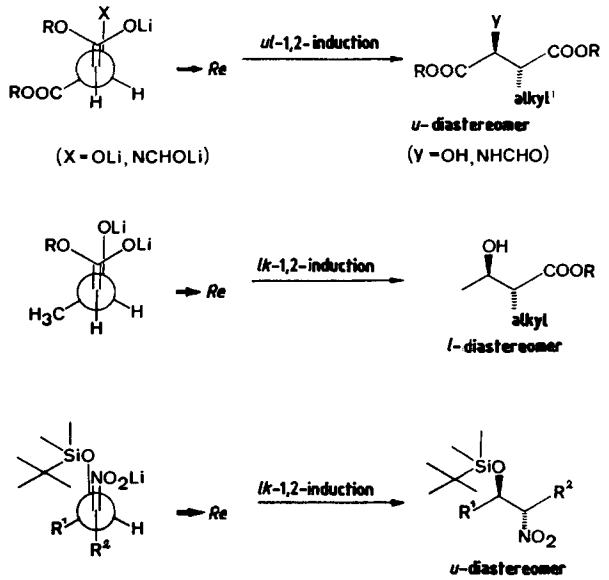


Scheme 7. 1,2- and 1,3-inductions in reactions of substrates with allylic and homoallylic structures.—In the last reaction all three types of processes specified in Scheme 4 occur: (1) formation of a new CC bond between two trigonal centers; (2) addition to a double bond; (3) a 1,3-induction. Notice that the cyclization follows the rule of "antiperiplanar hydrogen atoms" with respect to both double bonds (see 15 in Scheme 11)[8].

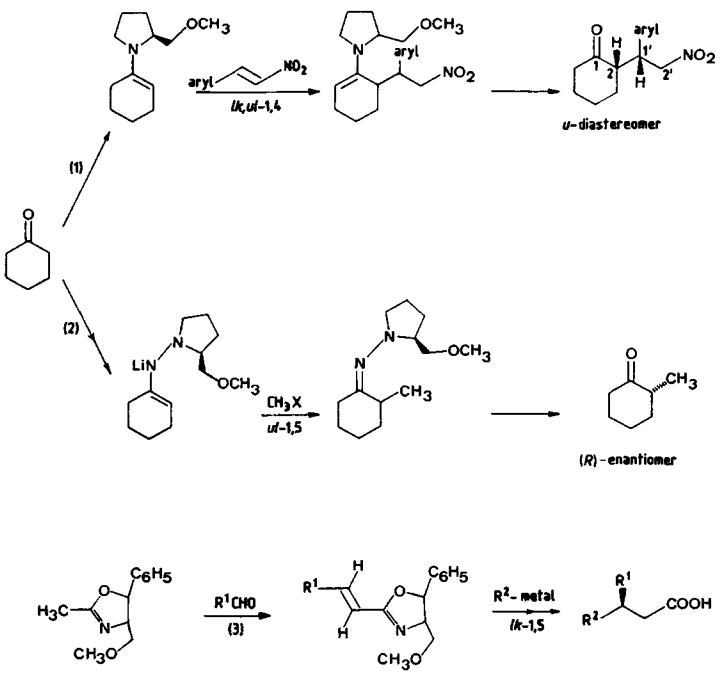


Scheme 8. Specification of reactions following the Cram or Prelog rule. With the normal priority order of substituents at the inducing and at the trigonal centers, both the open-chain [$CO > R^1$, $CH(CH_3)R^1 > CH_2R^2$] and the cyclic [$OR^2 > CO > R^1$] models of the Cram rule have the relative topicity *l* [approach from the *Re*-face of the (*R*)-enantiomer or from the *Si*-face of the (*S*)-enantiomer (see first three equations of the scheme)]. Similarly, the Prelog rule always describes processes with relative topicity *ul* [priority order $R_L > R_S$ (fourth equation)].

metric syntheses. Three such reactions are described by the equations in Scheme 12. In the Horeau method of kinetic resolution[40] an (*R*)-alcohol reacts preferentially with the (*R*)-acylating reagent, a like-selectivity. In the so-called "immolative" asymmetric synthesis[20] of an alcohol by re-

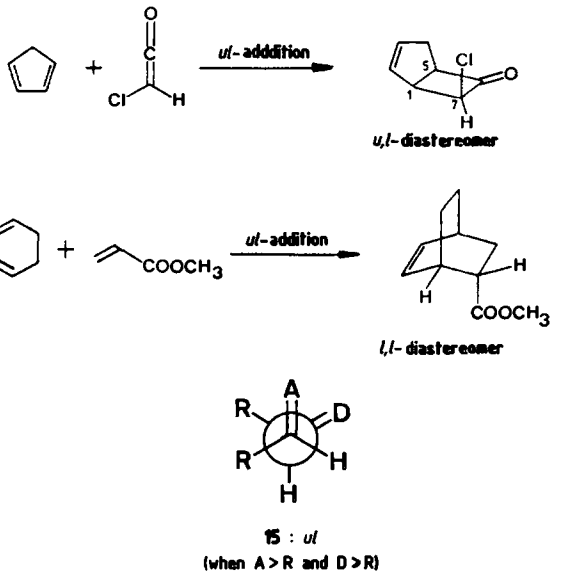


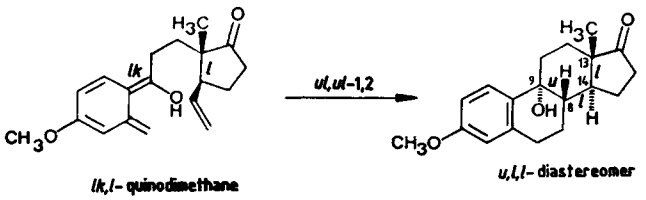
Scheme 9. Specification of three reactions following a rule for electrophilic addition to donor double bonds (cyclic model). On comparison of the second with the third reaction, common features are revealed by the relative topicities rather than by the relative configurations of the products (OLi > C=C > CH_3 and OSi > C=N > R^1); cf. text for a comparison of the first two reactions.



Scheme 10. 1,4- and 1,5-Inductions in the side chain of heterocycles.—The "natural" enantiomers of the prolinol derivatives in reaction (1) and (2) are shown.—The intermediates given do not have to be isolable for specification of relative topicities: formation of (*R*)-methylcyclohexanone under the influence of the (*S*)-center of the heterocycle is a *ul*-process (cf. Scheme 12).—The substrate of reaction (3) contains two 1,5-inducing centers; the route of highest priority leads to the phenyl-substituted center which serves for the purpose of specification (cf. Scheme 4).

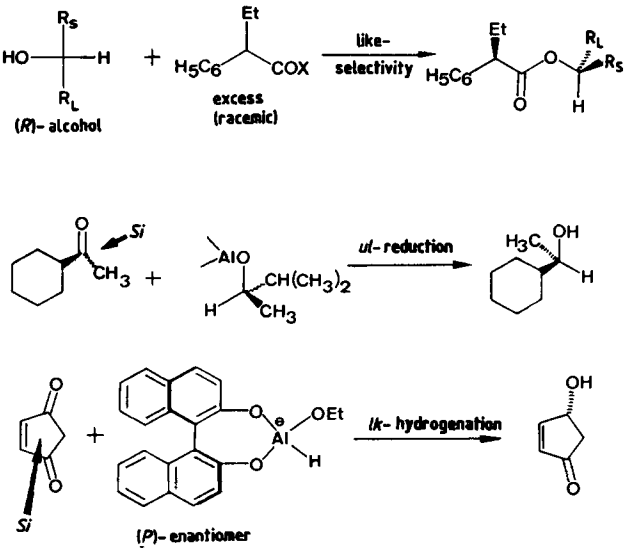
duction of a ketone with an enantiomerically pure aluminum alkoxide, the reducing reagent with (*R*)-configuration approaches the ketone from the *Si*-face[41], *i.e.* with unlike selectivity. If axes or planes of chirality, or helical structures[28] are formed during a reaction or are present in one of the reactants, the convention proposed here can be ap-





Scheme 11. Specification of relative topicities of cycloadditions.—Notice that the *endo*-additions of chloroketene and of acrylic ester turn out to have *ul* relative topicities—just like the preferred mode of nitroaldol and aldol additions (see Scheme 6). All of these reactions are in agreement with the "H-antiperiplanarity rule" [8], see **15** (cf. also third equation in Scheme 7).

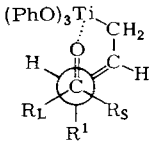
plied by extending the meaning of "like" to the combinations (*R,M*), (*S,P*), (*M,Re*), and (*P,Si*), and of "unlike" to (*R,P*), (*S,M*), (*P,Re*), and (*M,Si*). By means of this extension, the "enantioface differentiation"[42] by an axially chiral aluminate reducing reagent, shown in Scheme 12[43], is *lk*.

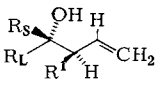


Scheme 12. Application of the like/unlike-specification to asymmetric syntheses, which are not included in the general types (1)—(3) of Scheme 4.

4. Conclusion

Current procedures for specification of the steric course of diastereoselective reactions are often arbitrary and ambiguous. In this paper we propose a slight extension of the CIP-system for specifying the steric course in terms of *relative topicities* and configurations of reactants and for the specification of relative configuration of the product. The advantage of specifying *relative topicity* rather than product configuration is that the former more often discloses similarities and differences in the steric course of reactions (see Scheme 13). The reason is not hard to find: the number of ligands at the stereogenic centers is smaller.





R_L	R_S	R^1	% *ds* [14]	Relative Topicity	Relative Configuration
$CH(CH_3)_2$	H	CH_3	96	*lk*	*u*
$CH(C_2H_5)_2$	H	CH_3	99	*lk*	*u*
$C(CH_3)_3$	H	CH_3	98	*lk*	*l*
$CH_2CH_2C_6H_5$	H	CH_3	95	*lk*	*u*
$CH(C_6H_5)_2$	H	CH_3	93	*lk*	*l*
C_6H_5	H	CH_3	85	*lk*	*l*
C_6H_5	H	C_4H_9	93	*lk*	*l*
C_6H_5	H	$CH(CH_3)_2$	98	*lk*	*l*
p-$CH_3C_6H_4$	H	CH_3	90	*lk*	*l*
p-FC_6H_4	H	CH_3	93	*lk*	*l*
p-$CH_3OC_6H_4$	H	CH_3	98	*lk*	*l*
p-NCC_6H_4	H	CH_3	80	*lk*	*l*
p-$O_2NC_6H_4$	H	CH_3	81	*lk*	*l*
C_6H_5	CH_3	CH_3	88	*lk*	*l*
C_6H_5	CH_3	C_4H_9	87	*lk*	*l*
C_6H_5	CH_3	$CH(CH_3)_2$	87	*lk*	*l*
C_6H_5	C_2H_5	CH_3	74	*lk*	*l*
C_6H_5	$CH(CH_3)_2$	CH_3	55	*lk*	*l*
$C(CH_3)_3$	C_6H_5	CH_3	98	*ul*	*l*
C_6H_5	$C{\equiv}CCH_3$	CH_3	72	*lk*	*u*
C_6H_5	$C{\equiv}CCH_3$	C_4H_9	77	*lk*	*u*
C_6H_5	$C{\equiv}CCH_3$	$CH(CH_3)_2$	77	*lk*	*u*
o-$C_6H_4(CH_2)_3$		CH_3	65	*lk*	*l*
1-Naphthyl	CH_3	CH_3	98	*lk*	*l*
n-C_6H_{13}	CH_3	CH_3	70	*lk*	*u*
Cyclohexyl	CH_3	CH_3	87	*lk*	*u*
Cyclohexyl	C_2H_5	CH_3	60	*lk*	*u*
$C(CH_3)_3$	CH_3	CH_3	96	*lk*	*l*

Scheme 13. Illustration of the usefulness of specifying the relative topicity by means of a further example of practical importance: the addition of 2-alkenyl(triphenoxy)titanium compounds to aldehydes and unsymmetrical ketones proceeds in such a way that the more bulky substituent R_L on the carbonyl C atom is orientated antiperiplanar to the allyltitanium part of the nucleophile which is anchored to the carbonyl O atom. With one exception, in all the cases shown the relative topicity is *lk*, whereas in 19 cases the product configuration is specified as *l*, and in 9 cases as *u* [44].

Different CIP-sequences of ligands will sometimes lead to different descriptors for reactions with analogous diastereoselectivity, but chemists familiar with the CIP-system will easily recognize them.

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tions *n* (negative). We prefer the abbreviations *l* and *u*, because *P* and *p* are reserved for specification of axial, planar, and helical elements of chirality [28].
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Synthetic Membranes—Preparation, Structure, and Application

By Wolfgang Pusch* and Axel Walch*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

After a long period of dormancy, membrane separation processes have begun to emerge as technically significant and commercially relevant unit operations. Prior to the mid-sixties, synthetic membranes were employed for those few specialized laboratory applications which could tolerate low permeability and poor selectivity or in electrochemical applications excluding, *e.g.*, batteries, fuel cells, chloride-alkali electrolysis, where marginal chemical stability remained a severe limitation. Within the framework of a broad R & D program started in the US in the mid-fifties and devoted to the production of fresh water from brackish and seawater, developments of more suitable membranes arose out of the application of the principles of physical chemistry, modern polymer chemistry (especially surface or interfacial polymerization and polycondensation technology), and electron microscopy. In particular, it was learned that asymmetric membrane structures comprise a very thin consolidated barrier layer (5000 Å or less for membranes with economically practical filtration rates) supported by an integral but less dense substrate which does not participate in the transport process. Later and after much effort, composite membranes were developed in which the salt-rejecting skin (still only 5000 Å thick) was placed atop a supporting matrix formed from a more chemically and mechanically stable polymer.—The main desalination research effort led to several spin-off developments in related membrane fields, *e.g.* the successful preparation and commercialization of ultrafiltration technology in the automobile, food, and chemical industries. Also, ion-exchange membranes prepared from perfluorinated polymers offered the electrochemical industry much better chemical stability than the earlier phenolic-resin-based ion-exchange membranes.—Current efforts are aimed at the improved selectivity and stability required for very specific separation processes (*e.g.* separation of heavy metal salts from waste water or selective enrichment of gases). In the future, the mechanisms of biological processes will have to be exploited for successful development of synthetic membranes suitable for more sophisticated separations.

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1. Introduction

Membranes continue to be the object of intensive research in the fields of physical and polymer chemistry, biology, medicine, and physiology[1-10]. Moreover, synthetic

membranes are being applied to the solution of process engineering separation problems in the pharmaceutical industry[13, 14], and in medicine for therapeutic (artificial kidney[11]) and diagnostic purposes (multilayer, thin-film colorimetric assay for clinical analysis[12]). Further impetus for the application of membranes comes from biotechnology where the substrates and/or products are concentrated and purified by means of synthetic membranes[15, 16]. In the food industry, and especially in the milk and whey processing segments, processes were modified early on to take advantage of membrane separation technology[17–20]. The success of such installations encouraged the textile and metal finishing industries to exploit similar technology for improved production efficiencies and for the solution of waste water problems. Membrane separation processes for recycling of electroplating effluents and for recovery of rinse waters containing water-soluble and lubricating oils are now fully established[21, 22]. Additional possibilities for process improvement were offered to the chemical industry by the cleaning of polymer latices, by the electrowinning of Cl_2 and NaOH by means of the chloride-alkali electrolysis process, and by concentration of specified components from the gas phase (gas separation[23–26]) and from solution *via* the vapor phase (pervaporation[27–29]). Additional fields for the application of synthetic membranes include the preparation of ultrapure water for the electronics industry[30], deacidification of natural gas[31], enrichment of O_2 for combustion processes[32], and last but not least brackish and seawater desalination[33–37] which has initially and decisively contributed to the progress of membrane technology during the past twenty years.

Table 1. Membrane separation processes, Δc = concentration difference; $\Delta\Pi$ = osmotic pressure difference; ΔE = electrical potential difference; ΔP = pressure difference.

Driving force	Process	Field of Application
$\Delta c(\Delta\Pi)$	Dialysis	Purification of polymer solutions (separation of electrolytes and low molecular weight non-electrolytes) Artificial kidney, controlled release
ΔE	Electrodialysis	Production of salt and of fresh water from brackish and seawater; reduction of acidity of citrus juices; processing of special galvanic waste waters (Cr-salt containing solutions); aqueous metallurgy of uranium
ΔP	Ultrafiltration	Purification and concentration of juices and polymer solutions; protein recovery from waste waters of dairy industry; waste water purification
	Hyperfiltration	Preparation of fresh water from brackish and sea water; purification of waste waters; recovery of valuable metal salts from galvanic industry waste waters
	Piezodialysis	Separation of electrolytes

The combination of applied research and practical experience from existing installations has led to the development of ecologically beneficial membrane processes which, for example, conserve energy and protect raw materials. Table 1 summarizes typical membrane processes along with their fields of application and the corresponding driving forces. Tables 2 and 3 contain a compilation of membrane processes used for the protection and recovery of raw materials, while Table 4 gives an overview of the medical applications of membrane processes.

Table 2. Membrane processes for raw material production.

Market segment	Raw material	Membrane process (Requirements on the membrane)
Chemical industry	Plastics	Micro-, ultra- and hyperfiltration
	Organic chemicals (Perfluoropropylene oxide)	Membrane electrolysis (current efficiency)
	Inorganic chemicals (chlorine, caustic soda)	Membrane Electrolysis (current efficiency)
	Boiler Water	Hyperfiltration
Pharmaceutical industry	Products of fermentation broth (antibiotics, proteins)	Microfiltration (reduced absorption capability)
	Plasma proteins	Ultrafiltration
	Vaccines	Ultrafiltration
	Enzyme products (saccharides, antibiotics)	UF and enzyme reactor (reduced absorption capability)
Milk and whey industry	Proteins	Electrodialysis (reduced absorption capability) Ultrafiltration
	Lactose (→ethanol)	Hyperfiltration (resistant to acids, bases, and oxidizing agents)
Food industry (sea water)	Fresh water	Ultrafiltration Hyperfiltration (temperature resistant, resistant to oxidizing agents)
	Salt	Electrodialysis (critical current density)
Fuels	Ethanol (separation of azeotropes)	Pervaporation (permselectivity [a])
Industrial gas	Hydrogen Helium Propylene	Gas separation (permselectivity [a])
Natural gas	Methane (marsh gas) (deacidification: CO_2, H_2O)	Gas separation (permselectivity)
O_2 Enrichment	Oxygen	Gas separation (permeability)

[a] Permselectivity is a preferred permeability of the membrane to one or more components of a mixture.

The wide variety of applications for membrane processes calls for synthetic membranes with widely differing properties and performance characteristics. The following are the principal considerations guiding the selection of an appropriate membrane for a particular separation process:

1. The mechanism of separation (*e.g.* sieve effects, electrochemical effects, and solubility).

Table 3. Membrane processes for raw material production—recovery of raw materials.

Market segment	Raw material	Membrane process (Requirements on the membrane)
Cellulose processing industry	Process water Chemicals Rinse water	Ultrafiltration Hyperfiltration (resistant to higher and lower pH and to chemicals)
Textile industry	Auxiliary substances Wash waters	Ultrafiltration
Automobile industry	Electroplating paints Rinse water	Ultrafiltration (reduced absorption capability) Hyperfiltration
Metal finishing industry (cutting and lubricating oils)	Ground and surface water	Ultrafiltration (resistant to solvents)
Membrane fabrication	Process water Solvents	Hyperfiltration (permselectivity)

3. Mechanical and chemical stability of the membrane.
4. Compatibility of the membrane with materials being processed [biocompatibility, absorption, and predisposition to the formation of deposits (*e.g.* membrane fouling and scaling)].

There are essentially three mechanisms of separation:

1. Separation based on large differences in the molecular sizes of the permeants (sieve effect).
2. Separation based on differences in the charges of the substances to be separated (salts or ions of different valencies, mixtures of electrolytes and non-electrolytes) (electrochemical effect).
3. Separation depending on the differences in solubility of materials in the membrane phase because of the physico-chemical features of the substances to be separated (*e.g.* polarity) (solubility effect).

Existing membranes are generally regarded as belonging to one of the three classes illustrated in Figure 1: coarsely porous, finely porous, or non-porous. When employed for

Table 4. Medical application of membrane devices. m = membrane.

Application	Process		Membranes	"State of the art"
Lung (oxygenation)	Blood	m: Air, CO_2, O_2	Silicone/polycarbonate Porous polypropylene (perfluoroacyl ethyl cellulose)	Clinical application
Kidney; blood (hemodialysis, hemofiltration, plasmapheresis)	Blood	m: Dialysate (filtrate) toxic metabolites (water)	Regenerated cellulose Cellulose acetate	Clinical application (clinical introduction)
Liver (hemoperfusion, cell perfusion)	Blood amino acids (con. bilirubin)	m: Adsorbent (hepatoma cells)	Poly-HEMA [a] Cellulose acetate Co-polyacrylonitrile	Clinical introduction (animal test)
Pancreas (cell implantation)	Blood glucose insulin	m: Langerhans islets	Modacrylic polymer [b]	Animal test
Skin (wound therapy)	Air H_2O O_2	m: Foam (gel)	Polytetrafluoroethylene Polyurethane (cellulose ether)	Clinical application
Eye (soft lenses)	O_2	m: Transcellular liquid H_2O	Poly-HEMA Silicone Cellulose acetobutyrate	Therapeutic application
Pharmaceutics (drug release systems)	drug	m: Extra-/transcellular liquid H_2O	Ethylene/vinylacetate-copolymer Cellulose ester	Therapeutic introduction
Metabolites (diagnostic systems)		m: Blood, transcellular liquid metabolites	Regenerated cellulose Cellulose ester	Diagnostic application

[a] Poly-HEMA = poly(hydroxyethylmethacrylate). [b] Modacryl = copolymer of *e.g.* 40% acrylonitrile and 60% vinyl chloride.

2. The permeation properties of the membrane towards the substances to be separated (volume flux and rejection of gaseous, dispersed or dissolved substances).

the separation of substances differing markedly in molecular size (salt from polymer for instance), such membranes should not interact strongly with either solvent or solute.

Such interactions may interfere with the sieve effect separation which depends upon geometric considerations alone[38]. Membranes possessing pore diameters larger than about 50 Å are usually considered as coarsely porous membranes. Therefore, a porous plug or glass frit might serve as prototype of a coarsely porous membrane. As long as electrokinetic effects are negligible, the volume flux

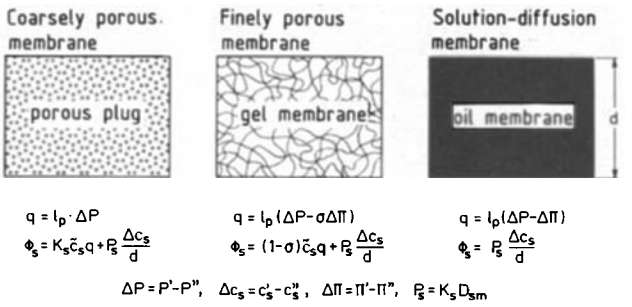


Fig. 1. Diagrammatic presentation of the prototypes of homogeneous synthetic membranes. $K_s = C_s/c_s$ is the solute partition coefficient, C_s the solute concentration within the membrane at the surface in contact with the external solution, c_s the solute concentration of the external solution, $\bar{c}_s$ an average solute concentration which can be calculated from the external concentrations c'_s and c''_s at both sides of the membrane, $P_s = K_s D_{sm}$ the solute permeability, D_{sm} the concentration-independent solute diffusion coefficient within the membrane, d the effective thickness of the membrane, $\Delta c_s = c'_s - c''_s$ the solute concentration difference across the membrane (driving force of the diffusive part of the solute flux), and q the volume flux, l_p = hydrodynamic permeability, σ = Staverman reflection coefficient [86].

across a coarsely porous membrane depends only on the hydrostatic pressure difference (ΔP) and is not affected by the osmotic difference ($\Delta\Pi$) since, *inter alia*, there is no interaction between the membrane matrix and the solvent. The solute flux Φ_s is composed of a convective part ($K_s \bar{c}_s q$) and a diffusive part ($(P_s/d)\cdot\Delta c_s$).

Substances differing in their valences and/or other physicochemical features can be separated by either a finely porous or a solution-diffusion (SD) membrane. Finely porous membranes possess pore diameters from about 10 Å up to about 50 Å. SD membranes either have no pores (liquid membrane) or behave as a homogeneous phase; for polymer films this means that the interstices between polymer chains of the membrane matrix are smaller than 10 Å. Hydrogels of lower water content (<30 wt.-%) are a good example of finely porous membranes. Most of the finely porous membranes (*e.g.* ion-exchange, cellulose, and cellulose acetate membranes) show a moderate to strong interaction between solvent (typically water) and the membrane matrix, which is observable, *e.g.*, by swelling of the membrane. As a consequence of this interaction, an effective osmotic pressure difference ($\sigma\cdot\Delta\Pi$) develops when such membranes are interposed between solutions with different solute concentrations; σ is the so-called reflection coefficient of the membrane to the solute as introduced by *Staverman*[39]. It commonly ranges from 0 to 1, but may also be negative[40–43]. In presence of a concentration difference across a membrane, the effective osmotic pressure difference causes a volume flux through the membrane (osmosis). The solute can be transported convectively ($(1-\sigma)\cdot\bar{c}_s q$) and diffusively ($(P_s/d)\cdot\Delta c_s$).

A film of oil, typically surrounding a droplet, is a good illustration of a SD membrane[44]. In the absence of pores there can be no convective transport. All components of a solution which are soluble in the membrane phase are transported across the membrane solely by diffusion (Fickian-, pressure-, and electro-diffusion)[45,46]. The SD model assumes that transport of each component follows only its own chemical (grad μ_i) or electrochemical potential gradient (grad η_i) in the membrane, *i.e.* it is assumed that the fluxes of the different neutral components (salts, non-electrolytes) are not coupled. Additionally, the classical SD model assumes that the pressure dependent portion of the chemical potential of the solute ($\bar{V}_i\cdot\mathrm{grad}\,P$; $\bar{V}_i$ = partial molar volume of solute within the membrane) is negligible in comparison to its concentration dependent part: $(\mathrm{grad}_c\,\mu_i = (\partial\mu_i/\partial c_i)_{T,P}\cdot(\mathrm{d}c_i/\mathrm{d}x))$. Given these assumptions, the solute is transported simply by Fickian and ultimately electrodiffusion. Figure 2 illustrates the application of these models to ultra- and hyperfiltration.

In addition to the pore structure, the ion-exchange capacity of a synthetic membrane affects its separative utili-

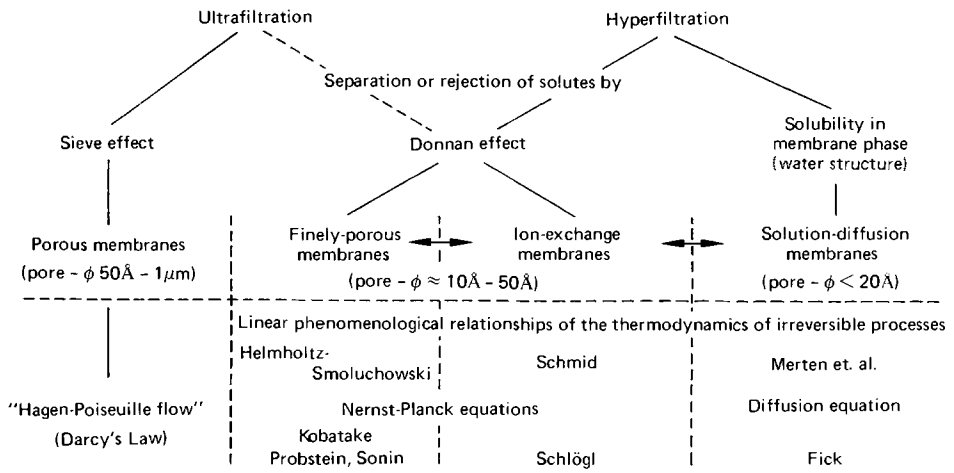


Fig. 2. Diagrammatic presentation of the basic transport mechanisms for synthetic membranes using ultra- and hyperfiltration as an example (pressure gradient; the pore diameter serves only as a guiding value) [86].

ty. By definition, ion-exchange membranes possess ionic groups (fixed charges), mostly covalently bound to the membrane matrix, whereas completely neutral membranes do not have ionic groups. The ionic groups of an ion-exchange membrane are subject to a dissociation equilibrium. Membranes whose substituted groups have a pK_a value between 3 and 9 are generally considered weak ion exchange membranes, those with larger or lower values are strong ion-exchange membranes. The fixed charge concentration of a strong ion-exchange membrane is rarely if at all affected by the pH value and the electrolyte concentration of the external solution, whereas the fixed charge concentration of a weak ion-exchange membrane strongly varies within certain ranges of external pH and electrolyte concentration[47-49]. At electrolyte concentrations smaller than the fixed charge concentration of the membrane, co-ions (ions with the same charge as the fixed charges) are excluded from the membrane phase on account of the Donnan equilibria at the phase boundaries between the membrane and the external solutions (Donnan exclusion). In the absence of electrical current through the membrane, counterions (ions possessing a charge opposite to that of the fixed charges) are also excluded from the membrane on account of the local electroneutrality condition within the membrane. Therefore, ion-exchange membranes reject salts and, in principle, can be employed for the separation of electrolytes from non-electrolytes. Ions may preferentially permeate an ion-exchange membrane when an electric current is applied as in the case of electrodialysis or when the membrane is composed of cationic and anionic regions (mosaic membrane) and thus exhibits electroneutrality *per se* (piezodialysis).

Very specific membranes (*e.g.* liquid membranes[53], microcapsules[54,55], and enzyme-loaded membranes) are used for special separation processes (*e.g.* extraction of heavy metal ions from very dilute solutions, enrichment of uranium, purification of waste gases by facilitated transport, control of enzyme reactions, and for diagnostic purposes in the public health service[50-52]). Liquid membranes are emulsions containing many microvacuoles suspended in an external solution. The ≈ 10 μm vacuole wall (liquid membrane) is an immiscible phase separating an internal solution (extraction or stripping solution) from an external solution (*e.g.* heavy metal ions to be separated or extracted). For example, when the internal phase of the vacuoles contains appropriate chelating agents, heavy metal ions will migrate from the external to the internal phase with enrichment factors reaching as high as 10^4. Instead of chelating agents, the internal phase may also contain enzymes or specific catalysts. Practical use of these liquid membrane suspensions firstly requires separation of the droplets from the waste solution and then the splitting of the emulsion into the droplet and the extraction phase, the latter containing the heavy metal ions. In order to circumvent this tedious procedure, supported liquid membranes are also available; they are prepared by soaking a porous membrane with the liquid membrane solvent loaded with a specific catalyst. Just as with liquid membranes, microcapsules possess an enormous surface area for mass transfer (10 mL of a suspension of microcapsules with diameters of about 20 μm possess a membrane surface of more than 2 m^2). They are made, *inter alia*, by encasing either an emulsion (*e.g.* enzyme containing solution) or a solid phase (*e.g.* active carbon) within a thin polymer film (*e.g.* cellulose ester). The solid phase is typically sprayed with the casting solution of the thin film. Enzyme membranes are prepared by physically or chemically fixing enzymes to an appropriate membrane matrix. Hydrophilic membranes, for instance those cast from cellulose and cellulose derivatives[56,57], exhibit minimal non-specific interaction with the enzyme, the substrate, and the product, and are thus preferred for the preparation of enzyme membranes. The enzymes can be attached to the membrane matrix by a variety of covalent and secondary bonds. Since this article is concerned only with commercial synthetic membranes such special, non-commercial membranes will not be dealt with any further.

2. Structure of Synthetic Membranes

During the early stages of membrane research, synthetic membranes were considered to be on the same level as sieves and sponges and essentially characterized by an average pore diameter or a pore size distribution[58-61]. Average pore diameters or pore size distribution curves can be established by means of mercury-intrusion, although only by assuming that the pores are cylindrical and at right angles to the membrane surface. However, prediction of the permeability behavior of synthetic membranes on the basis of average pore diameters or pore size distribution curves was not always successful. It was thus a great step forward when in 1949 *Hansmann* and *Pietsch*[62] succeeded in obtaining the first electron microscopic pictures of membrane filters. Subsequently, extensive electron microscopic investigations by *Helmcke*[63,64] led to a first classification of synthetic membranes according to their scale of porosity as either very finely, finely, or coarsely porous. *Maier et al.*[65,66], *Spandau et al.*[67] and more recently *Frommer et al.*[68] have partially elucidated the mechanism of membrane formation using information on the pore structure obtained from electron microscopic investigations.

However, it was not until the fifties that membrane research and development received major emphasis and funding from an extensive research program in the USA (Office of Saline Water, OSW) directed to the production of fresh water from brackish water and seawater. *Reid* and *Breton*[69] were among those who, extrapolating from past experience with osmosis and dialysis, tried to "press" salt water through membranes possessing an effective salt rejection and an adequate water permeability. They first demonstrated that cellulose acetate (CA) membranes are effective barriers for common salts. However, the water permeabilities of the approximately 5 μm thick CA membranes were too low for economic utilization in the production of fresh water.

Loeb and *Sourirajan*[70], who at almost the same time were studying the permeation behavior of commercially available CA membranes supplied by the Schleicher & Schüll Company, were the first to discover the possibility of an economic production of fresh water by means of synthetic membranes. The CA membranes used for their in-

vestigations possessed such a high water and salt permeability that they were originally considered useless for desalination of brackish water and seawater. However, when these membranes were annealed in a water bath at 75 to 95 °C, their salt permeability decreased considerably. Highly-annealed membranes acquired a high salt rejection, yet maintained a water permeability about one hundered times larger than that reported by *Reid* and *Breton*. It remained for *Merten et al.*[71,72] to clarify the structure of Loeb-Sourirajan membranes by electron microscopic investigations and thus to elucidate the mechanism by which the comparatively high water permeability and the low salt permeability coexisted. In contrast to the homogeneous membrane of *Reid* and *Breton* the modified membranes of *Loeb* and *Sourirajan* consisted of a very thin, dense layer of CA (active layer) resting on top of a porous supporting matrix. The active layer is comparable with a very thin homogeneous CA membrane. The supporting layer possesses negligible hydraulic resistance and is present for mechanical support only. The thickness of the active layer is about 2000 to 5000 Å out of an entire membrane thickness of about 100 μm. However, the water permeability of modified CA membranes when used for hyperfiltration at pressures of 50 bar up to 100 bar decreased continually with time. This phenomenon was principally a consequence of compaction of the porous matrix and the transition layer between the active layer and the porous matrix. Once the structure of asymmetric CA membranes had been clarified, a logical next step was preparation of membranes in which the very thin active layer was cast on top of a porous support made from a different and more pressure-resistant material. *Cadotte et al.*[73] and *Merten et al.* (see [74]) were the first to produce such composite membranes using originally membrane filters cast from cellulose nitrate and later very finely porous polysulfone membranes as supporting matrices. The supporting matrix was coated with a thin homogeneous film (*ca.* 1000 Å) of cellulose acetate. During manufacture the surface of the porous support was masked by a gel layer in order to prevent penetration of the casting solution for the thin-film into the pores of the porous support. Figure 3 illustrates the cross-section of a composite membrane. Several materials (*e.g.* polyamides,

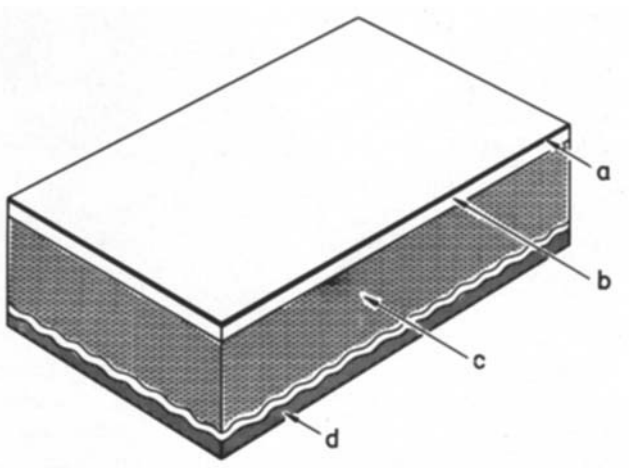
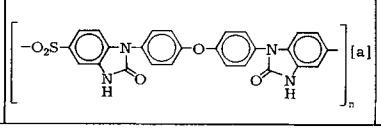
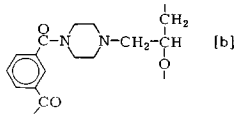


Fig. 3. Cross-sectional view of a composite membrane (schematic). (a) Thin film (active layer; 250–500 Å) of cross-linked polymer (PA-100 polyamide, PA-300 poly(ether-/amide), RC-100 poly(ether-/urea); (b) intermediate layer (gel) (PA-100, PA-300, RC-100); (c) porous supporting membrane; (d) reinforcing textile fiber [86].

Scheme 1. Evolution of Hyperfiltration membranes. Abbreviations for monomers and polymers: CTA: cellulose triacetate; CA: cellulose acetate; PPA: "polypiperazineamide" (cf. *e.g.* **2c**, Fig. 26); PEI: polyethyleneimine; IPC: isophthaloyl chloride; PBIL: polybenzimidazolone; PEC: poly(ethylene chloride); EDA: ethylenediamine; PIP: piperazine.

Period	Asymmetric membranes	Homogeneous membranes	Composite membranes	Progress
1953 (OSW)		Homogeneous cellulose ester membranes		Principal feasibility
1960	Asymmetric-CA membranes			Technical feasibility
1962	Spiral-wound (General Atomic)			
1965		CTA-hollow fiber (Dow)	CA-composites (Gulf)	Economic feasibility
1968	CA-blends (Aerojet)			
1969	N-Arenes (Du Pont, Monsanto)	Nylon hollow fiber (Dow)	Dynamic deposition (ORNL)	Flux, pH, more resistive to bacterial attack, rejection of solutes
1970		B5-hollow-fiber (Du Pont)	Plasma deposition (RTI)	
1971	B9-hollow-fiber (Du Pont)		Interface polycondensation/ cross-linking, PEI-IPC (NS-100/NSRI)	
	B-10 hollow-fiber (Du Pont)			
1972	PPA (Montecatini)			
1976			PEC-EDA-IPC (PA-300/UOP)	Low pressure membranes (temperature stability)
1977	PBIL (Teijin) [a]			
1978 (OWRT)			PBIL (Teijin) [a]	Resistive and selective towards organics (cleaning) [c]
1979			Plasma (Sumitomo)	
			PEC-PIP-IPC (Toray) [b]	
	 [a]		 [b]	(low fouling) [c]

[a] Repeat unit of PBIL. [b] Structural unit of IPC-, PIP and PEC-moiety. [c] Problems not yet solved.

poly(ether/amides), poly(ether/ureas), polybenzimidazolones; cf. Section 4.3.2) have been employed to form the active layer. It proved much easier to deposit permselective homogeneous thin-films, produced from appropriate polymers, on top of a tailor-made finely porous support than to cast a single polymer directly into a permselective asymmetric membrane. The development of membranes during the years 1953–1979 is summarized in Scheme 1 using hyperfiltration membranes as an example.

2.1. Electron Microscopic Investigations of the Pore Structure of Synthetic Membranes

Electron microscopy provides the only reliable tool for examining the microstructure and morphology of synthetic membranes. With the aid of electron microscopic pictures, it is possible to differentiate coarsely porous membranes from finely porous and dense (non-porous) membranes. In addition, membranes can be classified as homogeneous, asymmetric, or composite according to their structure. No pores are visible in electron microscopic pictures of finely porous and dense membranes; such materials nevertheless might possess pores with diameters ranging from a few Angstroms up to about 50 Å since these dimensions are not resolved by common electron and scanning electron microscopes. Figures 4–20 reproduce electron (EM) and scanning electron micrographs (SEM) of membrane surfaces and cross-sections. Figure 4 shows SEMs of the cross-sections of commercial cellulose membranes (®Cuprophan (4a, b) and ®Nadir membranes (4c, d)) principally used for artificial kidneys. ®Cuprophan films are cast from solutions of cellulose tetraamminecopper complexes, whereas

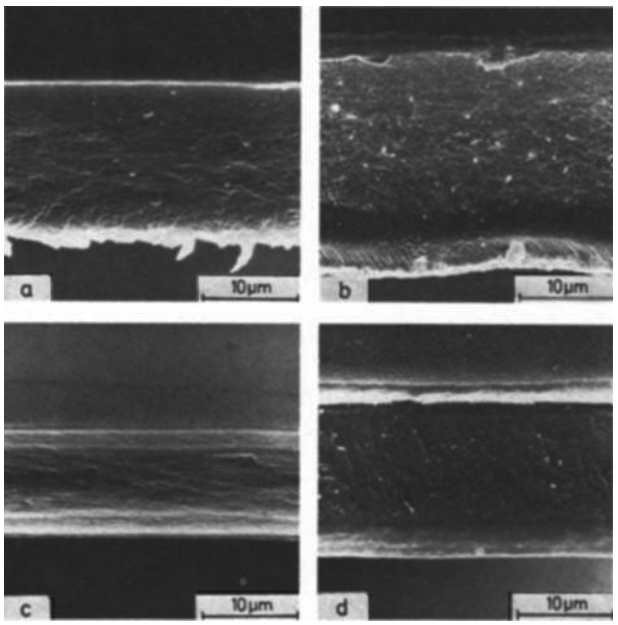


Fig. 4. SEMs of cross-sectional view (with a partial top view of one surface) of a ®Cuprophan (a, b) and a ®Nadir (c, d) membrane. The membrane samples used for the cross-section were directly immersed in liquid N_2 and then fractured (a, c), or the water of the samples was previously removed by the critical point method (b, d) [86].

®Nadir membranes are spun from viscose (cellulose xanthogenate solutions). The membranes are not completely homogeneous but rather possess surface layers clearly differing in structure from the internal homogeneous membrane matrix. Electron micrographs of cellulose membranes taken at large magnifications ($> \times 50000$) indicate pores with diameters of 40 to 60 Å in the inner membrane although the surface layers do not show any pores even at very large magnification. Cellulose membranes apparently consist of a fine porous matrix located between two dense (non-porous) surfaces (*ca.* 1000 to 3000 Å thick). Figure 5 shows similar SEMs of cross-sections of membranes cast from a polyacrylonitrile copolymer (5a) and a polycarbonate block copolymer (5b). These membranes, of which only the polyacrylonitrile membrane exhibits a fully homogeneous structure, are also used in artificial kidneys.

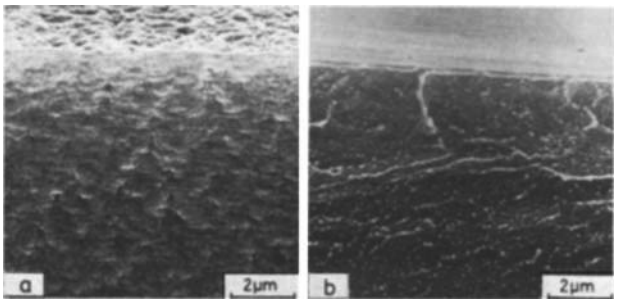


Fig. 5. SEMs of cross-sectional view (with a partial top view of one surface) of a symmetric hydrophilic gel-membrane made from an acrylonitrile copolymer (a) and an asymmetric, hydrophilic gel-membrane made from a polycarbonate block polymer (b), which are principally used as dialysis membranes [86].

Figures 6 to 8 show EMs and SEMs of the cross-sections and surfaces of the coarsely porous membranes typically employed for the concentration of polymer solutions and the separation of salts from polymer-salt solutions by ultrafiltration. There are two kinds of coarsely porous membranes: one group has a rather broad pore size distribution (Figures 6 and 7, "sponge structure"), whereas the other group has pores of nearly uniform diameter (narrow pore size distribution; Figure 8, "sieve structure").

The production of membranes with pores of uniform diameters originated from the belief that ultrafilters act like sieves and thus separate molecules according to their size. This one-sided view of the filter action of porous membranes continues to exist, even though it could be learned from the rudiments of membrane science that the permeation of molecules across porous membranes is mainly governed by interactions of the molecules with the pore walls of the membrane. For example, many attempts were made to fractionate polymers according to their molecular sizes using porous membranes with uniform pore diameters, even though *Ferry*[38] had pointed out in 1936 in his review article on ultrafiltration that factors completely different from the molecular size must govern the permeation of a molecule through a membrane. This is illustrated by SEMs of ®Nuclepore filters (Fig. 9) which were used for the fil-

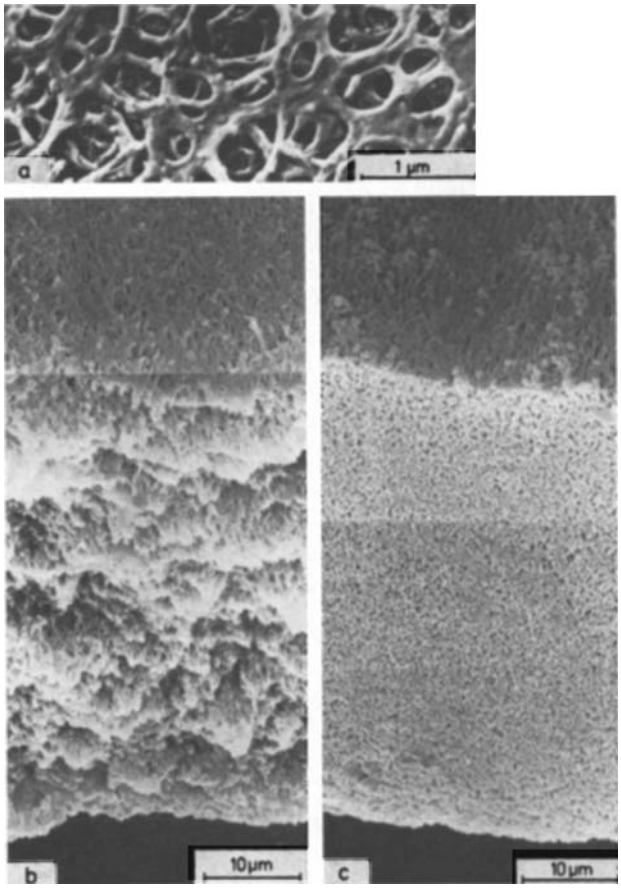


Fig. 6. EM of top view of a membrane filter made from cellulose nitrate (a) and SEMs of cross-sections (with partial top view of internal surface) of a porous cellulose diacetate capillary membrane (Asahi), unused (b) and after use for plasmapheresis (c) [86].

tration of polystyrene dispersions. The diameters of the polystyrene particles are clearly much smaller than the pore diameter of the membrane used (*ca.* 1 : 10). Neverthe-

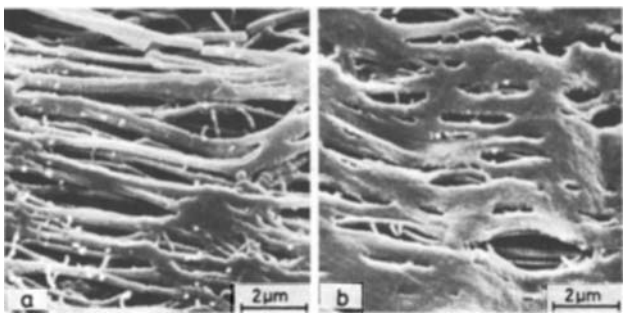


Fig. 7. SEMs of top (a) and bottom (b) surface of a Celgard 2400 membrane.

less, the polystyrene particles are nearly completely rejected as they adhere to the pore walls and thus the pores become progressively blocked.

This interpretation is supported by further SEMs (Fig. 10) showing surfaces of ®Nuclepore filters after their use for filtering erythrocytes. Although the dimensions of the erythrocytes are somewhat larger than the pore diameter of

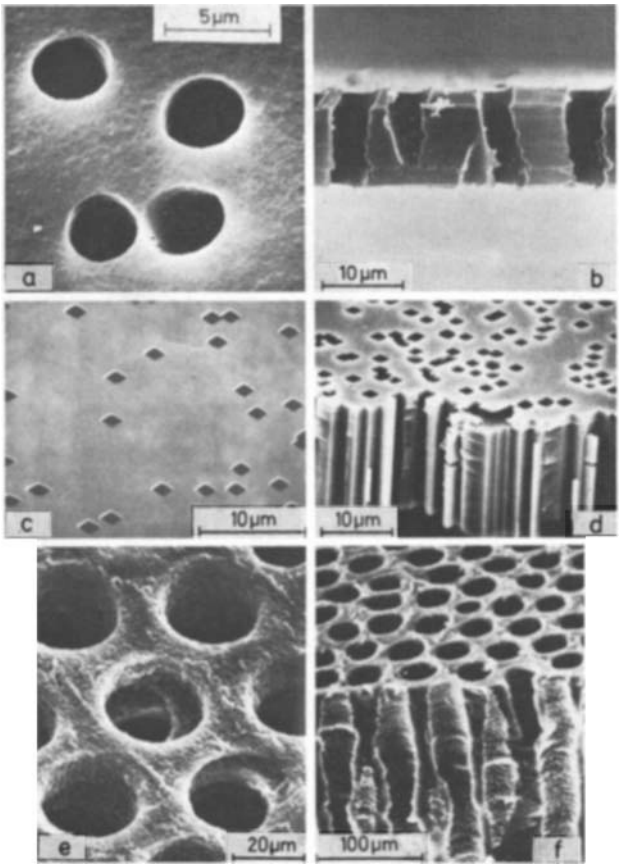


Fig. 8. SEMs of top (a, c, e) and cross-sectional (b, d, f) view of ®Nuclepore (a, b), mica (c, d), and Thiele membrane (e, f) [86] (cf. Section 3).

the membrane filter used, they pass the pores as they are flexible and scarcely interact with the pore walls. Both examples demonstrate that interactions between permeating

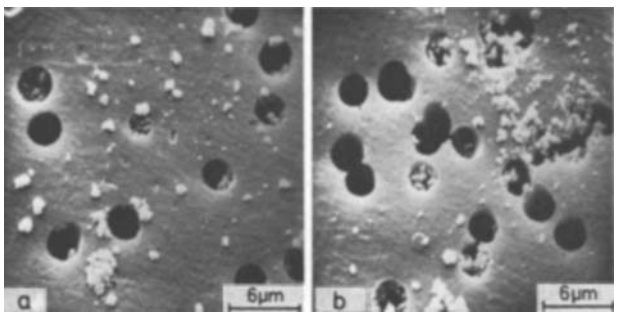


Fig. 9. SEMs of top view of ®Nuclepore filters used for the filtration of polystyrene particles [86].

molecules and the membrane matrix are more important in determining ultrafiltration behavior than the "theoretical" dimensions of molecules or particles.

Figures 12 and 14—20 show SEMs of cross-sections of asymmetric and composite membranes. All these membranes consist of an extremely thin film (active layer) on top of a more or less porous supporting framework (matrix). In the case of asymmetric membranes, the porosity of the supporting matrix increases across the membrane from top to bottom. The pore diameters, the shape of the pores, and

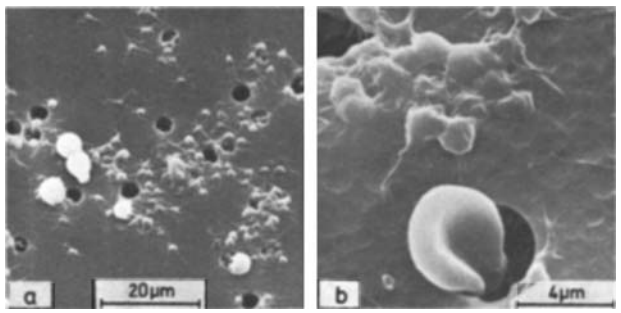


Fig. 10. SEMs of surfaces of ®Nuclepore filters used for the filtration of erythrocytes. The agglomerated erythrocytes are artefacts which were not present during filtration but formed during the preparation of the membrane samples for electron microscopic investigation [86].

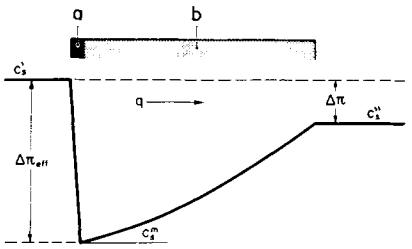


Fig. 11. Schematic presentation of the concentration profile across an asymmetric membrane when a concentration ($\Delta c_s = c_s' - c_s''$; $c_s' \leqslant c_s''$) and a pressure difference (ΔP) are applied causing a volume flux $Q = A \cdot q$ from the (')-phase to the (")-phase (A = effective membrane area) [147].

the porosity of the supporting framework can be varied within certain limits by adjusting the composition of the casting solution and conditions of membrane fabrication.

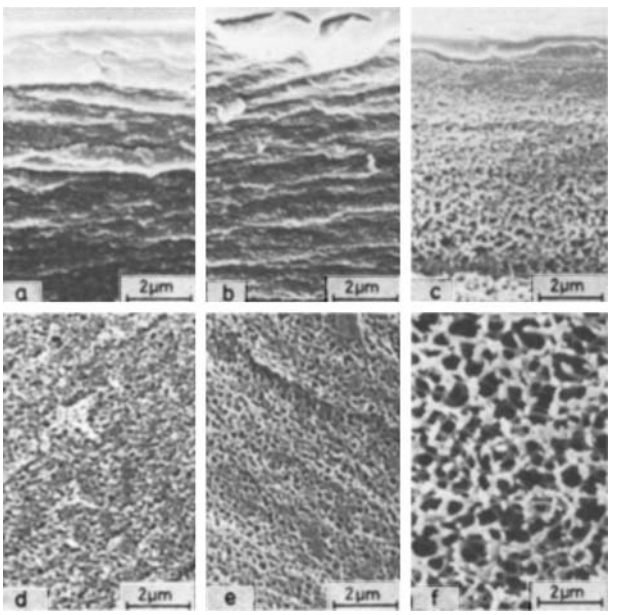


Fig. 12. SEMs of cross-sectional view of asymmetric cellulose acetate (CA) membranes. The upper row (a, b, c) exhibits a partial top view of the active layer and the junction between the surface and substructure. The lower row (d, e, f) displays the bottom part of each membrane. Figures a and d show the top and bottom part of an asymmetric CA membrane annealed at 85 °C; Figures b and e exhibit the top and bottom parts of the corresponding unannealed membrane; Figures c and f are an unannealed asymmetric CA membrane prepared from a casting solution formulated to yield highly porous membranes. The nominal molecular weight cutoffs are MW = 10000 (b, e) and MW = 100000 (c, f) [86].

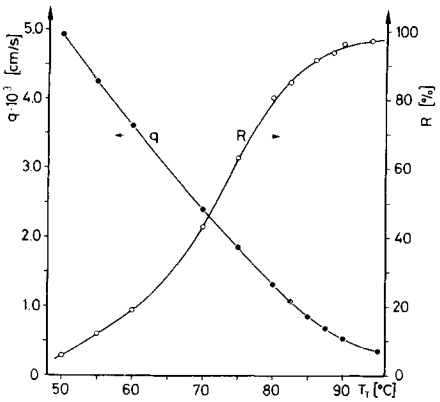


Fig. 13. Salt rejection R and volume flux q of an asymmetric CA membrane (manufactured by Kalle Niederlassung der Hoechst AG) at 25 °C as functions of the annealing temperature T_t; $R = r$ (salt rejection) × 100 [%]; $r = (c_s' - c_s'')/c_s'$; c_s' = brine concentration (= 0.1 M NaCl) and c_s'' = product concentration of the salt [75].

The transport properties of asymmetric and composite membranes in hyperfiltration experiments are exclusively

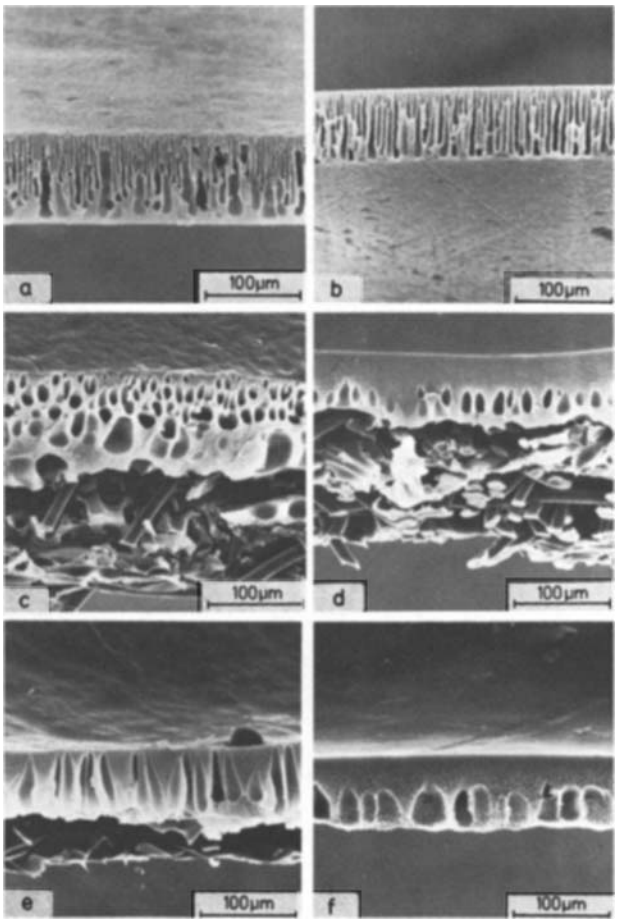


Fig. 14. SEMs of cross-sections (including partial top view of active layer) of typical PS membranes. Figures a and b show membranes with irregular (a) and regular (b) finger structures of the supporting framework where the interfacial tension at the surfaces of the corresponding casting solutions was different and the compatibility of the casting solutions with the precipitation baths was poor. Figures c–f display cross-sectional views of membranes with foam-like and finger structure (c, d, e) of the supporting matrix at low (c, e) and high (d) polymer concentration of the casting solution as well as medium (c, d) and good (e) compatability with the precipitation bath, and with foam-like structure and cavity formation (f) at low polymer concentration of the casting solution and a good compatability with the precipitation bath.

governed by the transport characteristics of the active layer. On the other hand, the support layer might strongly affect the transport properties of these membranes in dialysis-osmosis experiments because of so-called concentration polarization effects within the porous support[75,76]. In this connection, concentration polarization means the formation of a concentration gradient across the porous support (Fig. 11) affecting the solute concentration just at the junction between the active layer and porous support. Under the assumption that the reflection coefficient σ of the porous support is nearly zero (see Fig. 1), this concentration gradient affects the osmotic pressure difference across the active layer and thus the volume flux across the entire membrane.

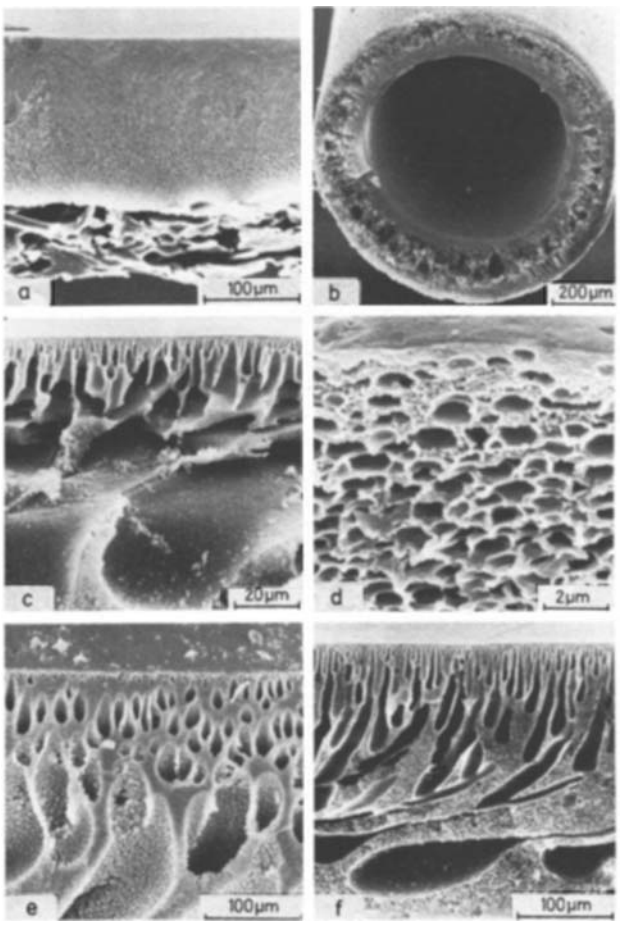


Fig. 15. SEMs of cross-sectional views (with partial top view of active layer) of asymmetric flat sheet (a, c, d, f), capillary (b) and tube membranes (e) fabricated from PS (a—d), modified PVDF (e), and PA (f) possessing only foam-like (a), foam-like and finger (b, c, e, f), and honeycomb (d) structure of the supporting framework. The fingers in the PA membrane (f) are strongly bent. The compatibility of the casting solution with the precipitation bath was good (a, b) and poor (c), Therefore, the asymmetric PS membrane shown in c exhibits large cavities.

Figure 12 shows SEMs of cross-sections of three different asymmetric CA membranes. The upper row exhibits a partial top view of the membrane surface (active layer) and the junction between the surface and substructure. The lower row displays the bottom part of each membrane. Figure 12a shows the cross-section of an asymmetric CA membrane, annealed at 85 °C; Figure 12b exhibits the cross-section of the corresponding unannealed membrane; Figure 12c shows an unannealed asymmetric CA membrane prepared from a casting solution formulated to yield highly porous membranes. Annealing of asymmetric CA membranes in a water bath at temperatures of 75 to 95 °C leads to a compaction of the membrane matrix (reorientation of the polymer chains) and thus to a decrease in its water and solute (salt) permeability (Figure 13). The decrease in the salt permeability corresponds to an increase in the salt rejection r ($R = r \cdot 100$). Figures 12 a–f illustrate the possibilities for varying porosity, its gradient across the membrane, and the pore structure over a wide range by proper selection of the composition of the casting solution and the casting conditions as well as of the annealing temperature. The properties of the active layer will also change when the casting solution and conditions are varied. In principle, it is even possible to change the relative positions of the active and porous layers by systematically varying the composition of the casting solution[77,78].

Figures 14—18 contain a number of SEMs illustrating cross-sections of typical asymmetric polyamide (PA), polysulfone (PS), polyvinylidene fluoride (PVDF) and polyacrylonitrile copolymer (PAN) membranes. In contrast to normal asymmetric CA membranes, the supporting matrices of these membranes possess, in addition to a foam-like pore structure, characteristic finger-like structures. The internal surface of the cylindrical, drop-, cone-, or

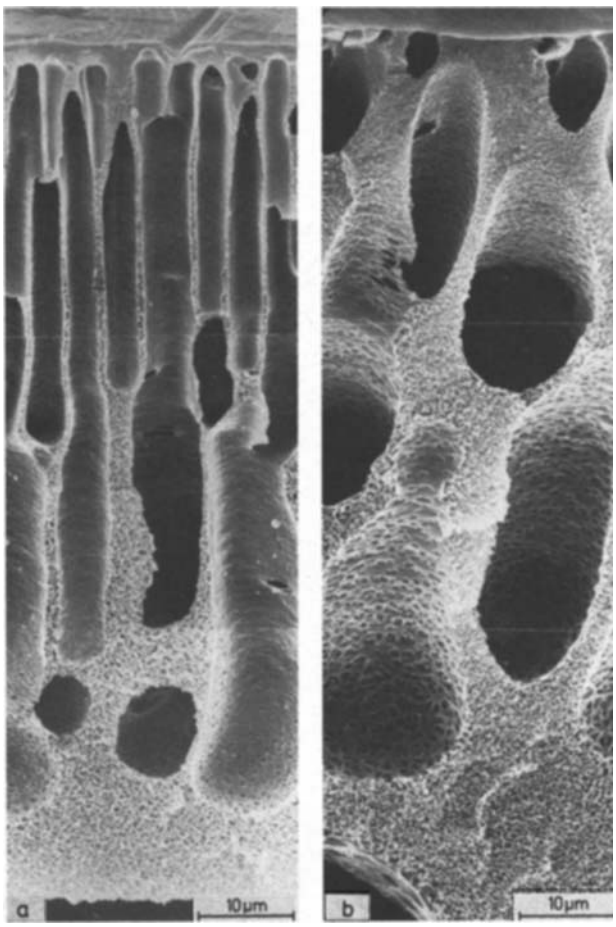


Fig. 16. SEMs of cross-sectional view of a PA (a) and a PS (b) membrane including partial top view of active layer.

needle-shaped[79] cavities may be porous or non-porous. The production of asymmetric PA, PS, and PAN membranes is complicated by the finger formation in the porous matrix since these fingers can extend into the active layer and create defects (Figs. 14c and 15e). It is possible but not usual, to cast asymmetric cellulose acetate[68, 80] and cellulose nitrate membranes[81] possessing similar finger-like structures. In contrast to CA membranes, PA and especially PS membranes are much more resistant to acids and bases, to microbes, and higher temperatures; PA membranes, however, are quite sensitive to chlorine, tolerating less than 1 ppm of Cl_2. The maximum working temperature for the membranes is, of course, not the same as that of the pure polymer but is determined by the gel structure of the membrane; the glass transition temperature of the solvated polymer is less than that of the polymer alone.

The transport of the components of a solution takes place within pores of the membrane scaffolding as well as across the finger-like cavities whereever the internal lining membrane of the cavities is porous (cf. Fig. 16). Therefore, the hydrodynamic resistance of these membranes is lower than that of asymmetric CA membranes possessing a comparable porosity. On the other hand, when the internal lining membrane of the cavities is dense and impermeable, the solute and solvent are transported through the extrastitial phase only. The permeation rate also decreases when the fingers are bent due to membrane formation or aftertreatment (Fig. 15e).

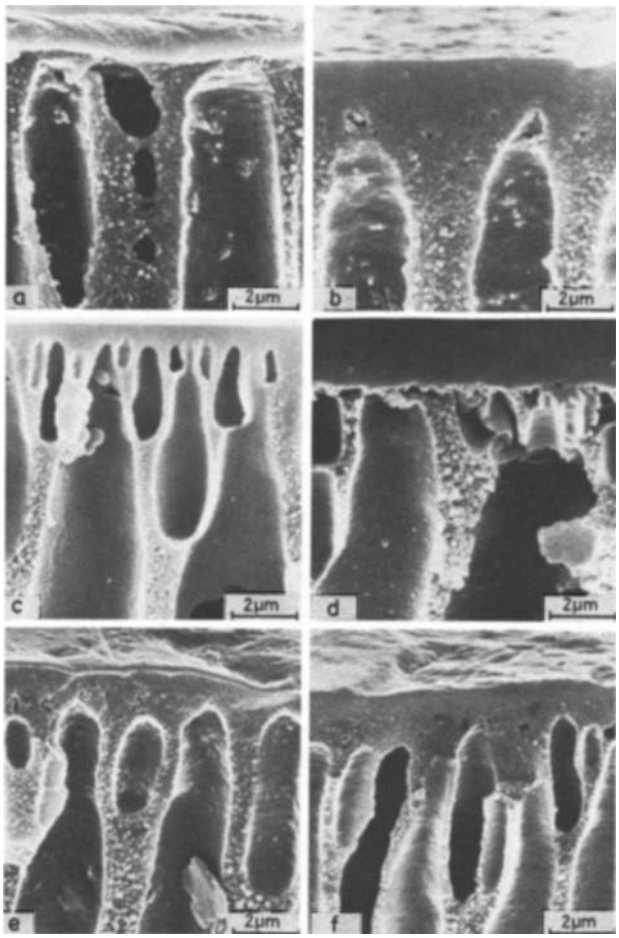


Fig. 17. SEMs of cross-sectional views showing the junction active layer/supporting framework of some PS (a–d) and PA (e, f) membranes. The membranes were cast from solutions of lower (a) and higher (b) polymer concentration and possess high (a) and low (b) porosity with large (a) and small (b) cavities. The PS membranes (c, d) were dried with (c) and without (d) glycerine added, yielding open porous (c) and closed porous (d) dispersed phases. The PA membranes exhibit a discontinuous (e) and continuous (f) transition of the active layer into the supporting framework. After precipitation, these membranes were stored wet (e) or dry (f) with glycerine added.

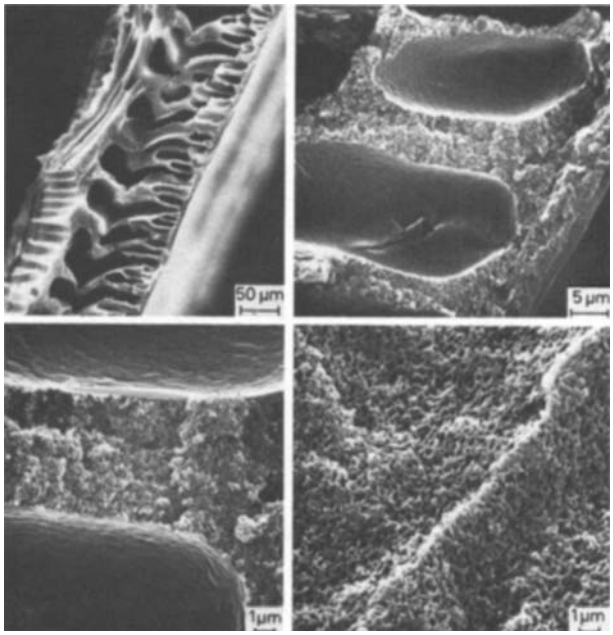


Fig. 18. SEMs of cross-sectional view of an asymmetric polyacrylonitrile membrane (Solrox-200 manufactured by Sumitomo Electric Industries, Tokyo, Japan) with foam and finger structure using graded magnification. (Stereoscan photographs by *Ch. Brücher*, Ciba-Geigy AG, Basel.)

Closing this chapter, SEMs of cross-sections of typical composite membranes are shown in Figures 19 and 20. Figure 19 shows cross-sections of two RC-100 membranes manufactured by UOP (Universal Oil Products, Fluid Systems Division, San Diego, Calif.) where the active layer is made from poly(ether/urea). The figures illustrate the different possible formations of the thin-film (active layer) on top of a porous matrix. In Figure 19a the transition layer of about 0.5 µm thickness becomes clearly visible whereas the active layer of about 250 to 500 Å thickness is not resolved. The active layer of this membrane was formed by coating, dipping, or interfacial polycondensation. In contrast, the just barely visible transition layer of the membrane shown in Figure 19b was formed by interfacial cross-linking. In this procedure, the porous support is soaked with the appropriate polymer solution and subsequently the polymer is subjected to a covalent cross-linking reaction at the membrane surface (see Section 4).

Finally, Figures 20 exhibit further SEMs of cross-sections of composite membranes. The porous support, usually PS, and the *ca.* 0.5 µm transition layer (gel layer) are visible, whereas the 250 to 500 Å thick active layer can only be seen in the top view.

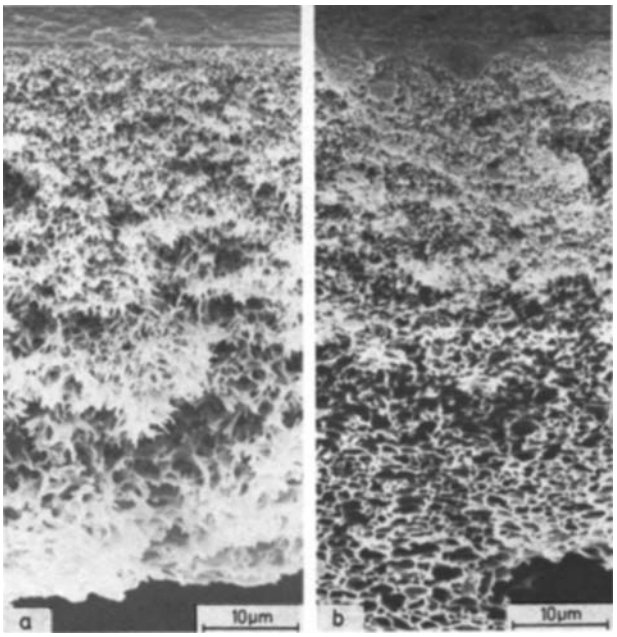


Fig. 19. SEMs of cross-sectional view (with partial top view of active layer) of two composite RC-100 membranes manufactured by UOP, San Diego, California, where the active layer is prepared from poly(ether/urea). The active layer in (a) was generated by coating, dipping or interfacial polycondensation, in (b) by interfacial cross-linking [86].

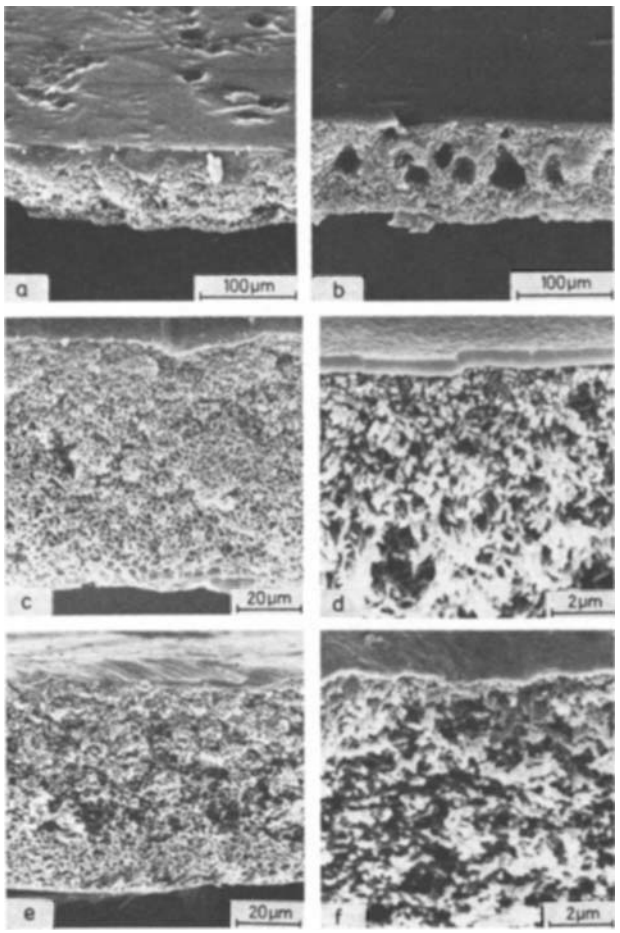


Fig. 20. SEMs of cross-sectional view (with partial top view of active layer) of composite PA-300 (a), Desal-LP (b–d; LP = low pressure, and RC-100 (e, f) membrane where the active layer is formed from poly(ether/amide) (a), a modified PA (b–d), and poly(ether/urea) (e, f). Using a 0.1 M NaCl brine solution at 25 °C, the Desal-LP membrane exhibits permeation rates of about 1500 to 2000 L m^{-2} d^{-1} and salt rejections of 92% to 96% at pressures of 15 to 25 bar [86].

2.2. Structure of Finely Porous and Dense Membranes

The pore structure of finely porous and dense (solution diffusion, SD) membranes can only be characterized by indirect methods such as gas and liquid permeation or gas sorption (sorption isotherms)[82–85] since the dimensions of interest are not resolved under the electron microscope. Thus, only model parameters are determined and these do not necessarily reflect the true physical and physicochemical membrane properties. This subject was discussed in detail in a recently published review[86] and need not be considered in more detail at this time. In addition to pore structure, the micellar organization and arrangement of polymer chains and chain segments (Fig. 21), for instance, as well as the physicochemical state of the polymer (crystalline, glassy, amorphous, *etc.*) play a decisive role in transport through finely-porous and dense membranes. Different mechanisms of gas permeation are found, for instance, below and above the glass transition temperature

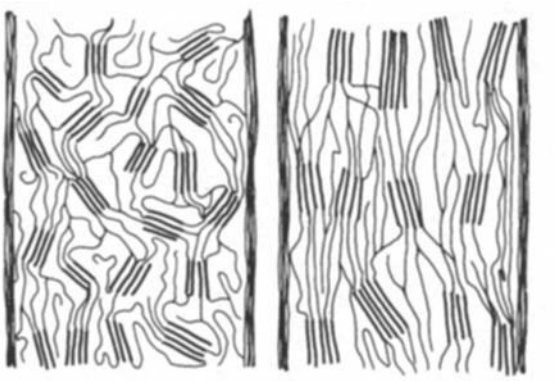


Fig. 21. Two figures illustrating the arrangement of amorphous and crystalline regions of polymer segments in semi-crystalline polymers [148].

of the constituent membrane polymer[87]. A summary of potential methods for the investigation of the molecular structure of synthetic membranes is given in Table 5.

Table 5. Methods for the characterization of the structure of synthetic membranes.

Microstructure (pore diameter < 50 Å)	Macrostructure (pore diameter > 50 Å)
Diffraction of slow neutrons Gas permeation with the help of the free-volume theory Gas adsorption using the BET isotherm, the dual-sorption model, and the free-volume theory Thermodynamic characterization of the water structure Thermomechanical analysis (TMA)	Electron microscopy Gas and liquid permeation using the Hagen-Poiseuille law and the Knudsen relationship Porosimetry (*e.g.* Hg-intrusion method) Bubble pressure method
Determination of the limits of molecular separation	
IR absorption spectroscopy	
X-ray scattering and diffraction ⟷	X-ray small-angle scattering
Differential thermoanalysis and scanning calorimetry (DTA and DSC)	

2.3. Water Structure in Synthetic Membranes

In addition to the membrane characteristics, the water structure within a synthetic membrane also governs transport mechanisms for both solutes and solvents[88-90]. For example, as long as free water exists along with so-called "bound water" within finely porous membranes, matter is transported primarily by convection and Fickian diffusion. On the other hand, if finely porous membranes and SD membranes contain only bound water, convective transport can be almost entirely excluded and the components of a solution will pass the membrane exclusively by diffusive processes (Fickian-, pressure-, and electro-diffusion). The water structure within a synthetic membrane may be characterized by NMR and IR spectroscopic investigations[91-94], by determination of thermodynamic data such as enthalpy, entropy, Gibbs free energy[95] of water sorption, and partial specific heat of water within the membrane[96-99], or by the water vapor sorption of the membrane. For example, it has been demonstrated that the partial specific heat of water within homogeneous CA membranes is always larger than that of free water (Fig. 22), indicating an interaction between water molecules and the polymer chains of the membrane matrix (hydrophobic interaction, H-bonds, dipole-charge interactions). This interaction of water with the membrane matrix decreases the

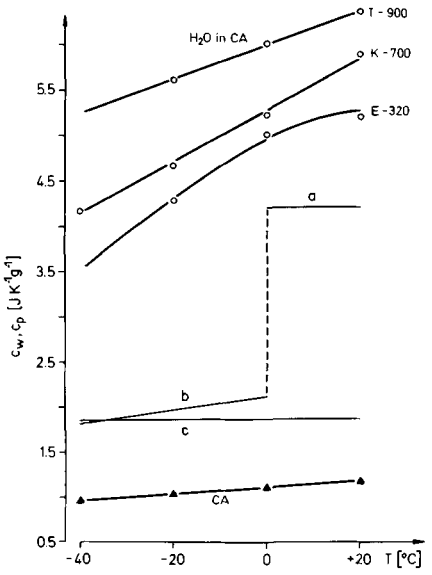


Fig. 22. Partial specific heat capacity of water c_w in homogeneous CA membranes of various acetyl contents as a function of temperature T. The specific heat capacities of water (a), ice (b), and water vapor (c) are shown for comparison. The acetyl contents of the CA membranes are: 32 wt.-% (E-320), 39.1 wt.-% (K-700), and 43.7 wt.-% (T-900) [96, 97].

available energy of hydration per water molecule, *i.e.* reduces the capacity of water to hydrate ions. Electrolytes and non-electrolytes are thus poorly dissolved and their sorption and transport is correspondingly inhibited. However, the water-polymer interaction is not so strong as to completely immobilize the water molecules. Thus, water transport can still occur by so-called activated diffusion.

3. Formation of Synthetic Membranes

The formation of synthetic membranes can, somewhat arbitrarily, be characterized by the following three mechanisms:

1. Formation of a polymer film by extrusion of the polymer material, by desiccation of a corresponding polymer solution (dry spinning process), or by *in-situ* polymerization and polycondensation.
2. Formation of a gel layer by a sol-gel transition.
3. Production of surface modified porous inorganic membranes (glass and ZrO_2/carbon capillaries) or of thin porous sheets of inorganic materials such as mica laminates creating pores by bombardment with heavy ions and subsequent etching of the nuclear tracks (cf. Fig. 8c, d[100]).

The formation of films from binary polymer solutions according to Method 1 yields homogeneous dense membranes without pores. Porous membranes can be produced by this method only by use of heterogeneous systems (*e.g.* addition of extractable fillers; ®Accurel). Moreover, it is possible to create pores in an as-cast polymer film by aftertreatment, *i.e.* mono- or biaxially stretching the film (®Celgard, ®Goretex, ®Poreflon) or bombarding the film with neutron-induced nuclear fragments or heavy ions, and subsequently etching the nuclear tracks (®Nuclepore filter).

Gel formation (Method 2), on the other hand, generally yields an asymmetric membrane where the porosity and its gradient across the membrane can be varied from very finely to coarsely porous by adjusting the composition of the casting solution and by selection of the conditions for gel formation. *Maier* and *Scheuermann et al.*[65,66] investigated the mechanism of membrane formation and discovered that the formation of pores within gel-membranes is closely related to the formation of coacervates in colloid solutions which was extensively researched and reported, *inter alia*, by *Bungenberg de Jong* and *Kruyt*[101]. Coacervate formation is a kind of segregation in colloidal solutions which does not yield two macroscopic phases (as could be observed in phenol-water mixtures) but rather a dispersion where one phase is colloidally dispersed in a second phase (coarse emulsion)[101]. Accordingly, a coacervate-like separation must occur during the production of porous gel-membranes. It can be induced by temperature variation, or by bringing the polymer-solvent film into contact with a non-solvent or poor solvent for the polymer. The non-solvent may be introduced to the polymer solution in the following four ways:

a) the non-solvent or poor solvent, which acts as a swelling or precipitation agent, is added to the polymer solution *via* a saturated vapor phase. Coarsely porous membranes are prepared by this procedure with a slight gradient of porosity across the membrane. Various membrane filters are prepared by this method[102].

b) The casting solution is formulated to contain both strong solvent(s) and poor or non-solvent(s) for the polymer (ternary and quaternary systems are preferred). The strong solvents are selected to be most volatile and are preferentially evaporated from the casting solution during membrane formation. When a critical polymer concentration is reached during the evaporation period, phase sepa-

ration will occur leading to the formation and agglomeration of solvent rich polyhedrally-shaped droplets. In a further step, an enrichment of the polymer occurs at the points of contact of the polyhedrally arranged droplets. Because of the concurrent dilution of the remaining droplet wall and the contraction pressure of the droplet, the vacuole system (pores) will open and the enclosed liquid will be "discharged". Alternatively, the droplets may be stable enough not to burst under these forces. This latter kind of membrane, which still contains packed spheres (nodules) in the final state, was first reported by *Cabasso et al.*[103]. Such membranes have good pressure stability since spheres, in contrast to droplets, do not collapse under pressure.

c) The polymer solution is cast into a film and directly or after a short evaporation period (period of contact with air or another gas phase) immersed into a "precipitation" bath containing a liquid (usually water) which is a non-solvent for the polymer but is miscible with the other components in the casting solution. The phase separation described above does not take place before the as-cast film enters the precipitation bath.

d) Production of ionotropic gels from polyelectrolyte solutions by diffusion of appropriate counterions into the polyelectrolyte sol (Thiele membranes[104]; Fig. 8e, f).

Asymmetric membranes with an active layer are frequently prepared by method c, or by a combination of methods b and c where the interfacial tension is one factor determining the relative thickness of the active layer. The thickness of the active layer as well as the pore structure of the supporting membrane can be controlled by the composition of the casting solution, its viscosity and polymer concentration, the duration of the period of contact with the gas phase, and the conditions of precipitation (phase separation) (for typical examples see Section 4).

Firstly, the pore structure of synthetic gel membranes will depend on solubility effects such as the "quality" of the solvents and the "power" of the precipitation agent[105–107]. The "quality" of a solvent can be graduated, for instance, by mixing (blending) a good solvent (for the polymer) with a weak or non-solvent. Ultimately however, the pore structure is determined by the kinetics of phase separation (similarly to crystallization processes from solutions). This may, in turn, be manipulated by adding salts (preferentially Li-salts) or polyelectrolytes to the casting solution to vary its viscosity and to control the kinetics of phase separation (*e.g.* by associate formation). Moreover, the action of the precipitation bath can be varied by presence of additives and by temperature changes. According to *Grethlein*[108], membrane formation thus depends on so many parameters in such ways that no quantitative statements can be made regarding the effect of the individual parameters and even qualitative statements possess limited validity for a specified system. Experience gathered from casting flat sheet, tubular, or hollow-fiber membranes, with a given polymer cannot be readily applied to other casting solutions. Nevertheless, a few general qualitative statements are possible:

Formulation of a casting solution with a strong solvent for the polymer promotes the formation of more dense membranes.

Rapid phase separation, which will result from "powerful" (highly immiscible) precipitation agents, contributes to formation of a thinner and more compact active layer and might also lead to finger-structures in the substrate.

The quicker the phase separation occurs the more likely it is that the internal surface of the fingers (if any) will be porous.

Higher polymer concentration or casting solution viscosity reduces the formation of fingers and cavities.

Employment of a weak solvent for the polymer and/or a weak precipitation agent leads to membranes with a limited asymmetry in their porosity *i.e.* small gradient of the porosity across the membrane.

The formation of the dense, homogeneous active layer of asymmetric membranes requires considerable enrichment of the polymer concentration relative to its level in the casting solution. This is accomplished by selection of an appropriate interfacial tension and partially by evaporation of the solvent from the surface of the as-cast film prior to precipitation. During preparation of hollow fibers with an active layer at the external surface of the fibers, the residence time is controlled by the length of the air segment through which the fiber leaving the spinneret has to pass before entering the precipitation bath. As no sol-gel transition occurs during the formation of the active layer, the resulting membrane consists of a thin-film (active layer) continuously merging into a gel-membrane (porous supporting framework).

4. Preparation of Typical Synthetic Membranes

Initially, virtually all synthetic membranes were cast from cellulose **1** (Fig. 23) and cellulose derivatives since these polymer materials were readily available and were

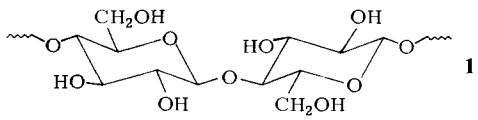


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Fig. 23. Cross-section from the structural formula of cellulose **1**.

known to be good film-forming substances[109]. After dissolving cellulose or its derivatives in appropriate solvents, a variety of techniques can be employed to cast thin-films or gel-membranes of *ca.* 1 to 1000 μm in thickness from the viscous solutions on appropriate supports.

®Cuprophan membranes are obtained when cellulose is dissolved as tetraamminecopper complex[110], then precipitated again from this solution by use of NaOH, and subsequently regenerated by means of H_2SO_4. In contrast, ®Nadir is spun from viscose solution (cellulose xanthogenate) which is precipitated in an acidic precipitation bath and subsequently regenerated into cellulose. The permeability of the as-cast membrane may be adjusted by mechanical or chemical aftertreatment[111]. Nowadays, membranes made from regenerated cellulose are used primarily for hemodialysis (artificial kidney) and also in "technical" dialysis

processes such as concentration and purification of protein solutions. Some typical physicochemical properties of cellulose membranes are listed in Tables 6 and 7.

night. (Unannealed homogeneous CA membranes exhibit a larger flux decline in hyperfiltration experiments at 50 to 100 bar during the first two weeks of operation.)

Table 6. Solute permeabilities P_s of some typical membranes of thickness d (concentration 0.1 wt.-%) at $T = 25\,^{\circ}C$. Membranes of this kind are used for artificial kidneys. Dextran T-20 (M.W. ≈ 20000) cannot permeate any of the membranes.

Membrane Designation	Material	d [μm]	MW:	$P_s \times 10^6$ [cm²/s] [c] Glucose 180.2	Saccharose 342.3	Raffinose 594.5	Urea 60.06	Creatinine 113.1	Vitamine B_{12} 1357.4	Inulin 5200
CMC [a]	Carboxymethylcellulose	29		0.888	0.487	0.286	2.63	1.31	0.187	0.0198
PT-150 (Bemberg)	Regenerated cellulose	32		0.744	0.531	0.340	2.30		0.263	0.0334
PM-150 (®Cuprophan)	Regenerated cellulose	25		0.930	0.560	0.410	2.50	1.50	0.0723	—
CA-260 [a]	Cellulose acetate	139		2.66	2.38	1.30	6.90	2.66	1.55	0.259
CA-260a [a]	Cellulose acetate	119		2.18	1.74	1.00	4.42	1.89	0.856	—
PM-200 (®Cuprophan)	Regenerated cellulose	34		ß.584	0.414	0.214	1.85	1.92	0.0974	—
GL-50 (®Nadir)	Cellulose regenerated from viscose	86		1.27	0.828	0.770	2.65		0.393	0.118
G-90 mod. (®Nadir) [b]	Cellulose regenerated from viscose	70					5.13	3.25	0.436	0.134
SG-45 (®Nadir)	Cellulose regenerated from viscose	32					2.93		0.422	0.101

[a] Prepared at the Max-Planck-Institut für Biophysik, Frankfurt am Main. [b] Modified at 37 °C. [c] In each case the quoted permeabilities were measured on one membrane sample. They deviate from sample to sample (50–100%).

Table 7. Membrane parameters (cf. Fig. 4).

Membrane parameter	®Cuprophan tube		®Nadir tube		®Cuprophan film		®Nadir film	
Designation	100	HDF	LG	HG	100 PM	HDF	LG	HG
Diameter of tube [mm]	100	30	100	30				
Wet thickness d [μm]	48	37	38	38	24	48	19	24
Plasticizer [wt.-%] [a]	27	45	23	56	12	40	20	54
Hydrodynamic permeability $l_p \times 10^5$ [cm/s·bar]	5.4	14	5.5	13	6.2	16	6.6	20
Normalized solute permeability, $(P_s/d) \times 10^4$ [cm/s]								
Urea	6.8	10.5	6.8	9.7	8.3	9.0	11.7	15
Vitamin B_{12}	0.6	1.2	0.6	1.2	0.8	1.2	1.0	1.8
Burst pressure, wet [N/cm²]	3.5	1.5	3.6	3.5	2.2	2.5	1.4	1.2
Shrinkage in water [%]								
Transverse	0	−10	3	8	−8	−7	−3	2
Longitudinal	6	8	1	4	3	3	1	3

[a] For example glycerine.

Cellulose acetate (CA), another cellulose ester widely used in membranes, is obtained by reaction of cellulose with acetic acid in the presence of acetic anhydride (H_2SO_4 catalysis). This reaction proceeds almost to completion giving almost fully esterified cellulose (triacetate[112]). Cellulose acetates of improved solubility are obtained by hydrolyzing some (10%—30%) of the acetate groups (secondary acetates; *e.g.* cellulose 2.5-acetate, in which on average 2.5 of the 3 OH-groups are acetylated). Such CA materials are dissolved in acetone, chloroform, or dimethylformamide, or similar solvents, to form viscous solutions from which homogeneous membranes can be cast. A typical recipe is as follows: *ca.* 10 wt.-% CA (*e.g.* Bayer Cellit K-700) is dissolved in acetone with continuous stirring of the solution. This casting solution is filtered to remove undissolved components such as gel particles. Homogeneous CA membranes are then cast by pouring this solution onto a glass plate at 30 °C and relative humidity ≤30% using a doctor blade (slit width 100 to 200 μm). The drawdowns are maintained at 30 °C overnight to yield membranes with a thickness of 10 to 20 μm. The membranes are subsequently annealed in an oven at 110 to 130 °C, also over-

4.1. Preparation of Micro-Filters (Membrane Filters)

Microfilters (microporous filters) can be produced from cellulose nitrate (CN), CA, and CN/CA blends. A typical casting solution for porous CN membrane filters is prepared by dissolving CN (5 wt.-%) in a mixture of methyl acetate (54.2 wt.-%), ethanol (23.7 wt.-%), butanol (12.3 wt.-%), H_2O (3.3 wt.-%), and glycerine (1.5 wt.-%). The resulting solution is then cast into a film and the solvent allowed to evaporate. In a common formulation for the preparation of CA microfilters Bayer Cellit F-1000 (3.3 g) and L-1000 (2.2 g) are dissolved in a mixture of dichloromethane (50 mL), ethanol (50 mL), and H_2O (4 mL). The film is then formed by volatilizing the solvents (no contact with saturated vapor phase). Porous membranes can be similarly prepared from CA/CN blends dissolved in mixtures of acetone, 1-propanol, ethanol, glycerine, ®triton X, and H_2O[113]. Figure 24 shows EMs of carbon replicas of the top and bottom surfaces of typical microfilters cast from CN/CA blends[113]. Such microfilters characteristically exhibit only a weak asymmetry in their porosity across the membrane. Any skin which may have (inadverdently) been

formed on the membrane surface will disintegrate when the pores are opened. Definite and graduated conditions of temperature, humidity, and air circulation must be carefully observed since phase separation is initiated by evaporation of the solvent(s). For many years, only microfilters based on cellulose esters were commercially available. Microfilters from additional polymers (*e.g.* polyvinyl chloride, polyamide, polytetrafluoroethylene, polyvinylidene fluoride) have just recently been commercialized.

filtration is used not only for the purification or separation of suspended or dispersed substances in mixtures but also for the removal of oligomeric or macromolecular substances from solutions. Virtually all current ultrafilters are asymmetric porous membranes. For instance, a typical ultrafiltration membrane is manufactured from cellulose acetate by using a casting solution prepared from cellulose 2.5-acetate (25 wt.-% Eastman CA-398) dissolved in acetone (45 wt.-%) and formamide (30 wt.-%)[115]. The viscous

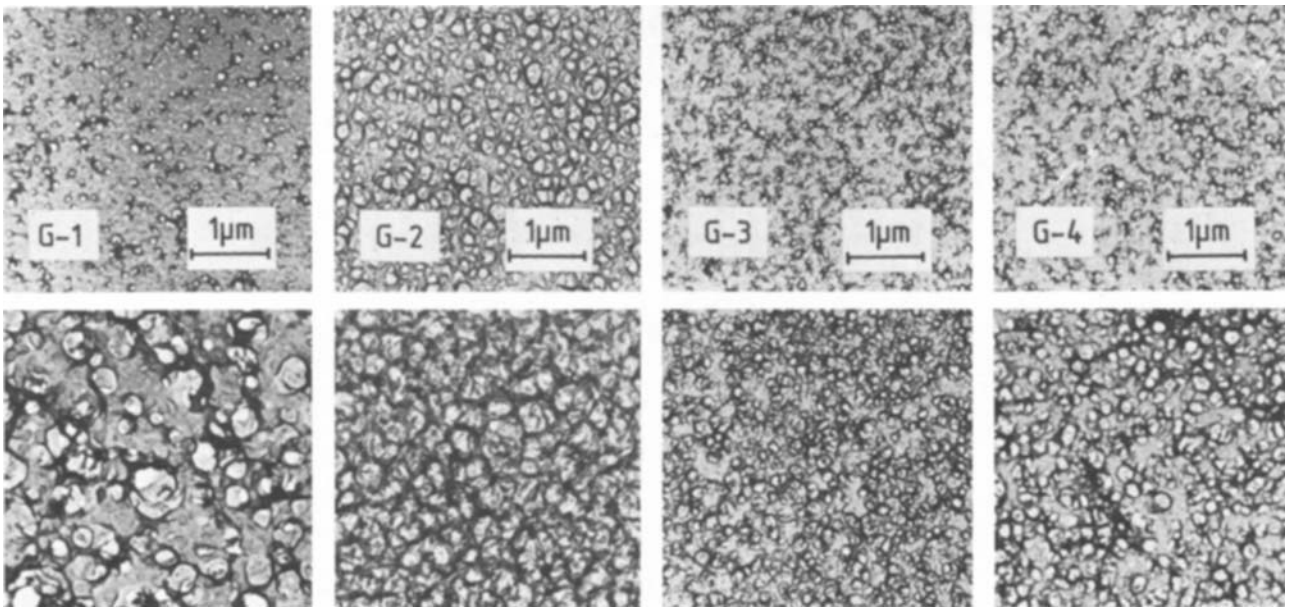


Fig. 24. EM pictures of preshadowed carbon replicas of the air-dried (upper row) and corresponding bottom (lower row) surfaces of asymmetric porous membranes prepared from CN/CA blends. Composition of casting solutions: CN : CA : acetone : 1-propanol : ethanol : glycerine : triton : water (wt.-%) = 8.5 : 1.5 : 60 : 23 : 4.5 : 1 : 0.5 : 1 (G-1); as G-1 but with a different CA material (G-2); 11.9 : 2.1 : 57.6 : 19.8 : 6.25 : 1 : 0.5 : 1 (G-3); 11.9 : 2.1 : 56 : 21.4 : 6.25 : 1 : 0.5 : 1 (G-4). Materials: CN HP-800 and Bayer-Cellit F-700 except for G-2 where Bayer-Cellit L-700 was used [86, 113].

Polysulfone (PS) is one additional polymer extensively studied for membrane application because of its chemical resistivity. Porous PS membranes were initially utilized as supporting matrices for composite membranes[114] since they are insoluble in several solvents commonly used to prepare the casting solutions of active layers. In addition to exhibiting chemical compatability, the supporting layer of composite membranes must combine high surface porosity with minimal pore diameters. This requirement is self-contradictory since the pore diameter of a gel-membrane generally increases with increasing porosity. However, satisfactory films were eventually achieved by very exact control of air temperature, humidity, and air flow velocity during the evaporation period and, also, by addition of surface active materials to the casting solution.

4.2. Preparation of Ultrafiltration Membranes

The production of ultrafilters (UF membranes) requiring a finely porous separative layer on top of the membrane was also initially based on cellulose esters, and these still play an important role because of their comparatively low material price and their good compatibility with biological materials, especially proteins. Unlike microfiltration, ultra-

solution is degassed under vacuum and then cast onto a glass plate using a doctor blade with a slit width of 100 to 200 µm. After a short evaporation period of only a few seconds, the polymer sheet is precipitated in a water bath (sol-gel transition). The membrane is then washed with water for at least 10 min to extract solvents and swelling agents. Asymmetric UF CA membranes with molecular weight cutoffs ranging from 5000 up to 20000 Daltons are formed using this recipe, the molecular weight cutoff primarily depending on the duration of exposure to air (evaporation period) and the temperature of the precipitation bath. A higher content of swelling agent in the casting solution affords more open (coarsely porous) membranes (higher molecular weight cutoff), whereas a larger proportion of solvent leads to more consolidated membranes (lower molecular weight cutoff). The phase separation, which takes place at the time of the immersion of the membrane into the precipitation bath, is essentially controlled by the ratio of solvent to swelling agent. The lower the content of solvent the faster phase separation occurs and this yields more open (coarsely porous) membranes.

UF membranes with a comparatively low molecular weight cutoff ($\leq$ 2000 Dalton) may also be prepared in this way, for example by annealing low porosity, as-cast films at 80 °C to consolidate the active layer. Cellulose acetate

membranes of graduated porosity, ranging from coarsely porous to finely porous and even to dense, can be cast by varying the casting solution, bath conditions, and aftertreatment. Membranes with low molecular weight cutoffs, bridging ultra- and hyperfiltration membranes, are of special interest for concentration and purification of peptides, hormones, and nucleotides.

Increasing attention is also being paid to other, more chemically and thermally stable polymers required for applications employing higher temperatures and more aggressive agents, *e.g.* in the food industry where membrane plants must be periodically sterilized and sanitized. The first generation of non-cellulosic UF membranes were made from polyelectrolyte complexes, modacrylic polymers, acrylonitrile copolymers, and polyamides; they are still being used for special purpose applications, *i.e.* certain molecular weight cutoffs or where non-specific absorption is a problem. Today, however, polysulfone and polyvinylidene fluoride (PVDF) membranes are preferentially used for ultrafiltration since they offer bettter temperature resistivity ($\leqslant 90$ °C), acid and base stability, and higher resistivity towards oxidizing agents (*e.g.* $\leqslant 2\%$ NaOCl).

Polysulfone, *e.g.* Udel 1700 manufactured by Union Carbide, is used for the production of porous PS membranes from casting solutions prepared from strongly polar, aprotic solvents[116] such as dimethyl formamide (DMF), dimethyl acetamide (DMA), *N*-methylpyrrolidone (NMP), or cyclohexanone, and occasionally swelling agents such as methanol. The casting process is the same as for CA membranes. The formation of the active layer (skin) as well as of the pore structure again depends on the viscosity of the polymer solution and on the interaction with the precipitation bath (hydrophilic-hydrophobic balance). Polymers such as polyethylene glycol (MW = 600) or polyvinylpyrrolidone (MW = 10000) are frequently added to the casting solution to yield a more dense and more foam-like pore structure by influencing the kinetics of precipitation (delaying phase separation). These rather lower molecular weight additives are extracted from the membrane in the precipitation bath[105].

The development of UF membranes thus began with the more hydrophylic polymers (*e.g.* CA, polyelectrolyte complexes) and progressively led to the use of more hydrophobic polymers (*e.g.* PS, PVDF). Application of these membranes in technical equipment to process increasingly diversified macromolecular or dispersed solution components (*e.g.* anaphoretic or cataphoretic electropaints, sweet or sour whey) requires UF membranes which will not absorb the dissolved or dispersed substances from the process system.

The hydrophilic/hydrophobic character of a polymer is also important when the membrane or complete system must be sterilized[117]. Attempts have been made during the

Table 8. Commercial ultrafiltration membranes and modules. Q = volume flux.

Membrane material [a]	Module [b]	Manufacturer	MW cutoff	Q [L m^{-2} d^{-1}]	Test conditions
Cellulose 2-acetate (HFA)	S, asym. T, *in situ*, asym.	Abcor	15000	6000 10000	3.5 bar, 50 °C, pH 3-7.5, 1 ppm Cl_2
Polyvinylidene fluoride (HFM)	S, asym. T, *in situ*, asym.	Abcor	10000/20000	7500 30000	3.5 bar, 90 °C, pH 2-9, 10 ppm Cl_2 (25 °C, pH 0.5-13)
Polytetrafluorethylene	F, sym.	Aqua-Chem.	50000	4000	5.6 bar, 100 °C, pH 1-14
Co-Polyacrylonitrile (HC-1, HC-5, HI-1)	C, sym.	Asahi Kasei Asahi Chemical Ind.	6000/13000	1000/4000	3 bar, 50 °C, pH 2-10
Polybenzoxazindione, sulfonated	F, asym.	Bayer	300	2000	40 bar, 50 °C, pH 2-12
Polyamide-/imide (BM)	C, asym.	Berghof/Nuclepore	2000-50000	100-6000	1.5 bar, 80 °C, pH 2-12
Co-Polyacrylonitrile/Vinylpyrrolidone	F, asym.	Daicel	30000	2000	3 bar
Cellulose acetate (800-500)	F, asym.	DDS	6000-65000	2000-7000	5 bar, 50 °C, pH 2-8, 0.002% NaOCl
Polysulfone (Gr 8/6/5 P, GS 81 PP sulfonated)	F, asym.	DDS	8000/20000/65000	1000-7000	3 bar, 80 °C, pH 0-14, 2% NaOCl
Modacryl polymer	P, asym.	Dorr-Oliver	18000/24000	3000/12000	2 bar, 50 °C, pH 2-11.5
Polysulfone	P, asym.	Dorr-Oliver	10000	10000	2 bar, 70 °C, pH 2-12
Cellulose acetate (Nadir)	F, T, asym.	Kalle } Membranes	2000-100000	400-10000	3 bar, 35 °C, pH 2-8, 0.002% NaOCl
Polyamide (Nadir)	F, T	Kalle } exclusively	20000-100000	2000-10000	3 bar, 65 °C, pH 2-12
Polysulfone (Nadir)	F, T	Kalle	10000-60000	1000-12000	3 bar, 90 °C, pH 1-14, 2% NaOCl
Polysulfone (PTUF)	S, asym.	Millipore	80000	2000	5 bar, 32 °C, pH 3-11
Polyolefin, hydrophilic	T, asym.	Nitto Electric	20000/100000	—	4 bar, 40 °C, pH 2-10
Cellulose acetate	F, W, asym.	Osmonics	1000/20000	1000/6000	3.5 bar, 27 °C, pH 2-8
Polysulfone	F, W, asym.	Osmonics	1000/20000	4000/12000	3.5 bar, 93 °C, pH 0.5-13
Cellulose acetate (T2-5A)	T, asym.	Paterson Candy	1000-20000		pH 3-6, 30-50 °C
Polysulfone (PM)	C, asym.	Romicon/Amicon	2000-50000	1000-14000	1 bar, 75 °C, pH 1.5-13
Modacryl polymer (XM/GM)	C, asym.	Romicon/Amicon	50000/80000	12000-15000	1 bar, 50 °C, pH 1.5-13
Co-Polyacrylonitrile/Methallyl sulfonate	F (Iris 3042)	Rhône-Poulenc	20000	7000	2 bar, 40 °C, pH 1-10
Polysulfone, sulfonated	F, asym. (Iris 3022)	Rhône-Poulenc	20000	15000	2 bar, 80 °C, pH 1-13
Carbon/ZrO_2	T, *in situ*	S.F.E.C.	50000	—	100 °C, pH 1-14
Polybenzimidazolone	T, asym.	Teijin	—	—	60 °C, pH 1-12
Polysulfone	T, asym.	Wafilin	5000	8000	3 bar, 95 °C, pH 1-12
Polyacrylonitrile	T, asym.	Wafilin	10000	7000	3 bar, 60 °C, pH 4-10
Cellulose (CUF)		Western Dynetics	20000	2500	1 bar, 70 °C
Polysulfone (PSUF)		Western Dynetics	20000	2500	1 bar, 80 °C

[a] The letters and/or numbers after some names signify tradenames or type designations. [b] Abbreviations: F = flat sheet, C = capillary membrane, P = plate, T = tube, and S = spiral-wound module.

entire course of membrane development to upgrade the hydrophobic character of membranes by introducing appropriate hydrophilic groups[118-120], the most successful example of which is the sulfonation of polysulfone[121,122]. Attempts were also made to blend appropriate hydrophobic polymers with hydrophilic ones. As different polymers are very often immiscible because of their positive enthalpy of mixing ($\Delta H > 0$) and their essentially small entropy of mixing ($\Delta S \approx 0$), considerable effort was required to develop miscible hydrophilic/hydrophobic polymer systems. For example, cellulose acetate is miscible with poly(phenylene oxyphosphate) esters[119,123] as well as with poly(4-vinylpyridine)[120]. In addition, PVDF and poly(vinyl alcohol) (PVA) can be blended if their poor miscibility is circumvented by use of poly(vinyl acetate) and its subsequent hydrolysis[124].

The interrelated aspects of boundary layer formation, interfacial tension, and non-specific adsorption are of particular importance in connection with ultrafiltration of complex physiological solutions such as blood (hemofiltration, hemodialysis, plasmapheresis, *etc.*). The volume flux of water *in vitro* is much larger than *in vivo*; this is not only due to the influence of special factors such as concentration polarization and the formation of secondary membranes (*e.g.* deposits of protein upon the original membrane), but also to the influence of the individual membrane polymer on the permeation behavior of the membrane in presence of more physiological solutions like blood.

Improved chemical resistivity towards a wide spectrum of organic solvents represents the most important potential improvement in UF membranes. This requirement is not readily achieved since the membrane formation process requires the polymer to be soluble in organic solvents. This problem might be resolved by cross-linking, after casting, polymer components of membranes composed from different soluble prepolymers (*e.g.* intermolecular cross-linked polyimide membranes). Porous inorganic membranes represent another possibility for improved solvent resistance. Such membranes are fabricated from porous carbon (by modification of its surface with ZrO_2[125]) and from porous glass (by phase separation of incompatible glasses[126,127]) and are preferentially shaped into tubular or capillary form. However, the comparatively high price of these products and the poor variability of their molecular weight cutoff limit their use. A complete list of commercial UF membranes and modules together with manufacturers is compiled in Table 8.

4.3. Preparation of Hyperfiltration Membranes

The principal uses of hyperfiltration are for the production of fresh water from brackish water and seawater, the preparation of ultrapure water, and the processing of service waters. Two requirements are paramount for fresh water production: the product water should contain a low concentration of salt (possibly WHO standards, *i.e.* ≤ 500 ppm salt) and the fresh water output should be as high as possible (*e.g.* 1000 up to 400000 m^3/d; see Table 9). The product water purity specifications will determine the properties of the membranes to be used, whereas the requirement

Table 9. Hyperfiltration plants (* 1980 under construction).

Application	Location	Capacity [$10^3 m^3/d$]	Module	Producer
Process water	Texas	1	hollow-fiber	Du Pont
Process water	Tarragone	1	hollow-fiber	Du Pont
Seawater	Bahrein	2	hollow-fiber	Du Pont
Brackish water	Robruk	2	hollow-fiber	Du Pont
Brackish water	Colorado	2	hollow-fiber	Du Pont
Ultrapure water	Warsaw	3	hollow-fiber	Du Pont
Boiler water	Tabriz	3	hollow-fiber	Du Pont
Ultrapure water	Mainz/Böblingen	3	hollow-fiber	Du Pont
Boiler water	Ginsby (GB)	5	hollow-fiber	Du Pont
Brackish water	Tobruk	6	spiral-wound	UOP
Brackish water	Florida	6	hollow-fiber	Du Pont
Cooling water	Basrah (Irak)	8	hollow-fiber	Du Pont
Process water	Algeria	9	hollow-fiber	Du Pont
Seawater	Jeddah	12	spiral-wound	UOP
Waste water	Orange County	20	spiral-wound	UOP
Waste water	Japan	> 10	spiral-wound hollow-fiber	Babcock, Du Pont
Ultrapure water	Japan	> 15	spiral-wound hollow-fiber	Babcock, Du Pont
Brackish water	Japan	> 60	spiral-wound hollow-fiber	Babcock, Du Pont
Brackish water	Peking	1*	hollow-fiber	Du Pont
Seawater	Caspian Sea	12*	hollow-fiber	Du Pont
Brackish water	Al Jubail	15*	spiral-wound	Hydranautics
Brackish water	Riyadh	50*	spiral-wound	Babcock
Brackish water	Mostaganem	46*	hollow-fiber	Du Pont
Brackish water	Riyadh	200*- 400*	hollow-fiber spiral-wound	Du Pont, UOP
Agricultural water	Yuma (Colorado River)	400*	spiral-wound	UOP, Hydranautics

for high daily output can only be met by a combination of highly water-permeable membranes with a comparatively large membrane area. This in turn requires high packing density (membrane surface area/module volume), which is obtained by appropriate membrane configurations in compact module constructions (plate and frame, spiral-wound, tube, and hollow-fiber modules). Plate and frame as well as spiral-wound modules require flat sheet membranes; tube modules require tubular membranes. The latter are prepared by either directly casting tubular membranes or shaping flat sheet membranes into tubular form. For the economic production of fresh water, plate and frame, spiral-wound, and tubular modules must be equipped with asymmetric or composite membranes (high water permeability). In contrast, in the case of hollow-fiber modules, which have more efficient packing density, one may employ either homogeneous or asymmetric hollow-fibers. The techniques given above for the preparation of homogeneous membranes from polymer solutions apply to hyperfiltration membranes as well and will not be repeated here. Only the preparation of typical asymmetric and composite membranes will be dealt with here.

Membranes for ultra- and hyperfiltration are prepared as flat sheet, tubular, and hollow-fiber membranes. Asymmetric hollow-fibers can be prepared with the active layer on either the inside or the outside of the fiber or both. Hollow-fibers employed for hyperfiltration have to withstand high pressures (*ca.* 30 to 70 bar) and generally have a relatively small inner fiber diameter so as to prevent collapsing. The bore diameter of the hollow-fine fibers used by the Du Pont Company in their B-9 and B-10 modules (for

brackish water and seawater desalination, respectively) is about 40 μm (Fig. 25d). To date, no hollow fibers are available for hyperfiltration where the brine is fed to the inside of the fibers. This would require an internal fiber diameter of 1 to 5 mm in order to approach economical flow conditions of the feed solution within the fibers. Moreover, when pressure is applied from the inside, a "self sealing" of the fibers in case of damage is impossible. Hollow fiber membranes, which cannot be supported as can flat sheet and tubular membranes, have limited mechanical stability and commonly function up to a few bar only, depending on their internal diameters; hence, their utility is limited to ultrafiltration. Figure 25 shows SEMs of the cross-sections of different capillaries and hollow fibers. In contrast to other viscose capillaries[128], also cellulose capillaries cast from viscose are completely free of imperfections and voids (for the status of hollow fiber preparation see [129]). As noted earlier, the selection of geometry for these membranes is chiefly dependent upon the feed solution to be processed.

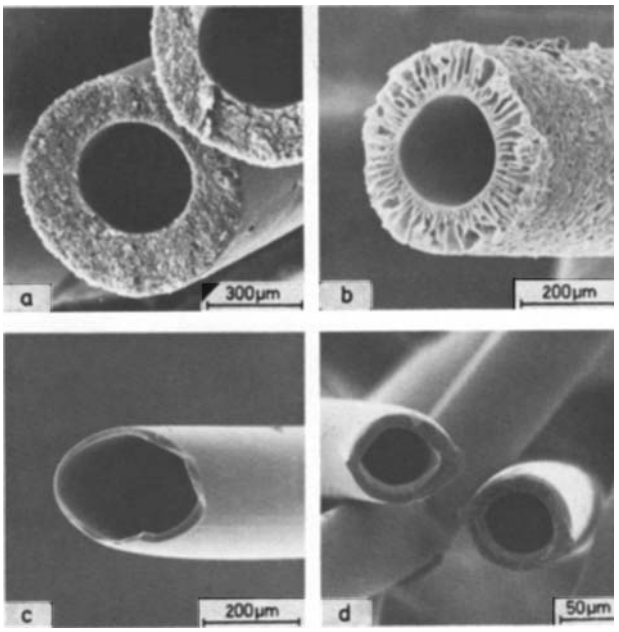


Fig. 25. SEMs of cross-sectional views of various capillary and hollow fiber membranes: symmetric, heteroporous microfilter from polypropylene (a; Membrana PP-105), asymmetric, heteroporous ultra/hemofilter from polysulfone (b; Amicon), symmetric and finely porous to dense hydrophilic gel-membrane from regenerated cellulose *e.g.* applied for hemodialysis (c; Kalle Niederlassung der Hoechst AG), and asymmetric, finely porous to dense polyamide hollow fiber (used for hyperfiltration) with the active layer on the outside surface (d; Du Pont B-9).

4.3.1. Preparation of Asymmetric Membranes

Most membranes are quite efficient substrates for the growth of bacteria and during use must be periodically sterilized. Cl_2 is the cheapest and most effective disinfectant, and desalination membranes should be able to resist Cl_2 concentrations of up to 20 ppm for short periods of time. CA membranes are the only practical material meeting this requirement. Therefore, cellulose acetates of varying acetyl content again have been the basic materials for the preparation of asymmetric desalination membranes. Asymmetric CA membranes are primarily cast from ternary or quaternary casting solutions. *Loeb, McCutchan,* and *Manjikian*[130] have prepared various casting solutions of CA in acetone and formamide, a typical example of which is CA (22 wt.-%), acetone (42 wt.-%), and formamide (36 wt.-%). After being filtered, the viscous solutions are subsequently cast onto a glass plate. During the evaporation period (30 to 60 s, which may be longer than for the preparation of UF membranes), the active layer is formed. Phase separation occurs when the film is immersed into the precipitation bath (water). The membranes remain in the water bath for 1 to 2 hours for solvent removal, and the water is repeatedly exchanged. The salt rejection of asym-

Table 10a. Commercial hyperfiltration membranes and modules from cellulose derivatives. Q = volume flux, R = salt rejection.

Membrane material [a] (Cellulose derivative)	Module [b]	Manufacturer	R [%]	Q [L m^{-2} d^{-1}]	Test conditions
-2.5-acetate	T, *in situ*, asymm.	Abcor	≤96	≥400	40 bar, 1% NaCl, pH 3-7, 35 °C
-2.5-acetate	S, asym.	Babcock (Ajax Int.)	95	700	40 bar, 0.5% NaCl, pH 4-6, 30 °C
-acetate, quaternated	S, asym., dry	Chem. Systems	99	500	68 bar, 1% NaCl, pH 4-8, 32 °C, 0.5 ppm Cl_2
-acetate	S	Daicel	—	—	—
-2.5-acetate	F, asym.	DDS	≤99	≥400	40 bar, 1% NaCl, pH 2-8, 30 °C
-3-acetate	H, sym., melt extraction	Dow Chem.	98.7	30	56 bar, 3.5% NaCl, pH 4-7.5, 35 °C, 0.5 ppm Cl_2
-3-acetate	H, asym.	Dow Chem.	97	200	28 bar, 0.3% NaCl, pH 6-8, 35 °C
-acetate, mixture	S, asym.	Envirogenics	98	1000	42 bar, 0.2% NaCl
	F, asym.		97.5	600	80 bar, 3.5% NaCl
-acetate-butyrate	asym.	Envirogenics	99.8	400	100 bar, 3.5% NaCl
-acetate, mixture	S, asym., dry	Hydranautics	95-97	1000-600	28 bar, 0.1% NaCl
-2.5-acetate (Nadir)	T, F, asym., dry	Kalle (only membranes)	≤98	≥400	40 bar, 0.5% NaCl, pH 3-7.5, 30 °C
-2.5-acetate	S, asym.	Millipore	90		14 bar, 0.1% NaCl
-acetate, mixture	T, asym.	Nitto Electric	93	—	50 bar, 3.5% NaCl
-acetate	F, W	Osmonics	≤99	≥400	56 bar, pH 2-3, 45 °C
-2.5-acetate	T, *in situ*, asym.	Paterson Candy	≤98	≥500	40 bar, 0.5% NaCl, pH 3-6, 30 °C
-3-acetate	F, asym.	Sartorius	99.8	<300	105 bar, 3.5% NaCl
-acetate	F, asym.	Schleicher & Schüll	≤99	≥400	80 bar, 3.5% NaCl, pH 4-7, 40 °C
-acetate	S [c]	Toray Ind.	96	300	56 bar, 3.5% NaCl, pH 4-7, 25 °C, 0.5 ppm Cl_2
-2-acetate	H	Toyobo Co.	93	—	30 bar, 0.2% NaCl, pH 3-7, 30 °C, 0.5 ppm Cl_2
-acetate	T	UOP	97	450	40 bar, 0.5% NaCl, pH 3-7, 45 °C
-2.8-acetate	S, composite	UOP	≥99	400	70 bar, 3.5% NaCl, pH 4-7.5, 35 °C, 0.5 ppm Cl_2
-2.5-acetate	T, asym.	Wafilin	≤96	≥700	40 bar, 0.5% NaCl, pH 3-8, 35 °C
-acetate	T	Western Dynetics	90	700	35 bar, 0.5% NaCl, pH 3-7, 40 °C

[a] The number preceding "acetate" signifies the average number of acetylated OH-groups per glucose unit. [b] Abbreviations, see Table 8. H = hollow fiber. [c] Tangential flow.

metric CA membranes can be adjusted by annealing the membranes in a water bath at temperatures between 75 and 95 °C, depending on the material; Eastman CA is annealed at temperatures of 75 to 85 °C and Bayer Cellit K-700 from 80 to 95 °C (see Fig. 13). Asymmetric CA membranes are cast into flat sheet and tubular membranes as well as into hollow fibers (Table 10a). The active layer can be produced at the inner or outer fiber wall. The poor chemical resistivity of asymmetric CA membranes and their susceptibility to hydrolysis, decreasing as the degree of acetylation increases, limit their application. Susceptibility to hydrolysis requires maintaining of a very narrow pH range ($5 \leqslant pH \leqslant 7$). In addition, common asymmetric CA membranes must either be treated with softeners before being dried or be stored wet.

Besides cellulose acetate, mixed esters such as cellulose acetate-butyrate, -palmitate, -acetoacetate, -methoxycarbonylpropionate, -dimethyl sulfamate, -hydrogen phthalate *etc.* have also been investigated regarding their suitability for the preparation of hyperfiltration membranes. *Cadotte et al.*[131] measured the transport properties of homogeneous membranes prepared from about 15 mixed esters of CA. Compared to CA, membranes prepared from the blends yielded either a lower salt rejection at better fluxes or a substantially lower flux at equivalent salt rejections.

CA membranes are precluded from many applications because of their susceptability to hydrolysis and biological degradation. After several false starts[132], development of membranes from completely synthetic polymers was finally successful. The Du Pont Company (Wilmington, Delaware)[133] and Monsanto-Chemstrand (Durham, North Carolina)[134] successfully prepared asymmetric membranes based on aromatic polyamides. The structural formulas of the basic units of polyamides and polar heterocyclic polycondensates used for the preparation of asymmetric membranes are compiled in Figure 26. Most polyamides are prepared by polycondensation (preferably low-temperature solution polycondensation) of complementary bifunctional compounds and cyclic or blocked monomeric intermediates (with two functional groups). The preparation of asymmetric membranes from the corresponding polyamides is fundamentally the same as that for asymmetric CA membranes. However, the evaporation periods for the solvents are longer since those used (*e.g.* dimethylacetamide (DMA), *N*-methylpyrrolidone (NMP), dimethyl sulfoxide (DMSO)) exhibit higher boiling points than, for example, acetone-formamide. Therefore, membranes drawn from viscous polyamide (PA) solutions, for example, are "dried" from about 5 min up to several hours in ovens with sufficient air circulation at temperatures ranging from 60 to 120 °C (PA solutions in DMA or NMP) or 80 to 160 °C (PA solutions in DMSO). Here also the active layer forms during the evaporation period. The "dried" membranes, still containing 15% to 75% of solvent, are then precipitated in a water bath at temperatures below 25 °C (phase separation). The membranes are then washed for several hours with water to remove all the solvents. The salt rejection and the water permeability of the membranes can be adjusted by varying the length of the evaporation period or by adding swelling agents (*e.g.* $CaCl_2 + H_2O$, butanol, cresol, glycerine, ethylene glycol, aromatic amides, *etc.*) to the casting solution. In contrast to asymmetric CA membranes, the permeation properties of asymmetric polyamide membranes are generally not improved by annealing.

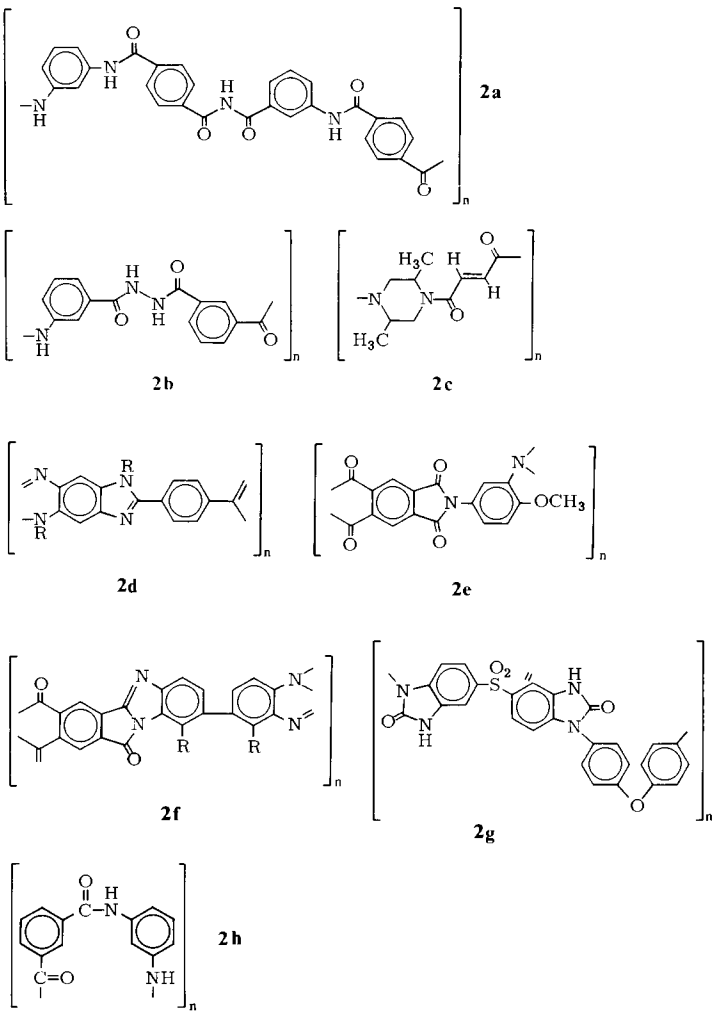


Fig. 26. Structural formulas for basic units of polyamides and polar heterocyclic polycondensates suitable for the fabrication of asymmetric membranes for hyperfiltration. Copolyamides **2a** (*e.g.* from terephthalic acid, *m*-aminobenzamide, *m*-phenylenediamine [149]), polyamide hydrazides **2b** (*e.g.* from isophthalic acid, *m*-aminobenzhydrazide [150]), polypiperazine amides **2c** (*e.g.* from fumaric acid, dimethylpiperazine [151, 152]), polybenzimidazoles **2d** (*e.g.* from terephthalic acid, tetraaminobenzene (substituted) [153], polyimides **2e** (*e.g.* from pyromellitic dianhydride, methoxy-*m*-phenylenediamine [154]), pyrrones **2f** (*e.g.* from pyromellitic dianhydride, diaminobenzidine (substituted) [155]), polybenzimidazolones **2g** (*e.g.* from diaminodiphenyl ether, dichlorodiphenylsulfone (substituted, cyclized) [156]), and *m*-phenyleneisophthalamide/terephthalamide copolymer (70:30) **2h** [133].

Polyacrylonitrile (PAN) copolymers have also been considered for the preparation of asymmetric membranes. However, the active layer in PAN membranes is generally too porous for use in desalination and only suited for ultrafiltration purposes. Recently, however, Sumitomo Electric Industries (Tokyo, Japan)[135] succeeded in obtaining a dense surface layer by plasma treatment of the porous surface. The asymmetric membranes prepared in this way exhibit volume fluxes of the order of 2000 to 3000 L m^{-2} d^{-1} at pressures of 80 to 100 bars and salt rejections for 0.1 M NaCl brine solutions ranging from 94 to 98% (see Table 10b).

Table 10b. Hyperfiltration membranes and modules from non-cellulosic material. Q = volume flux, R = salt rejection.

Membrane material [a]	Module [b]	Manufacturer	R [%]	Q [L m^{-2} d^{-1}]	Test conditions
Polysulfone, sulfonated	H, asym.	Albany	—	—	pH 2–13, 70 °C, 1 ppm Cl_2
Polybenzimidazole	H, asym.	Celanese	99.4 [d]	50	70 bar, 3.5% NaCl, pH 2–11, 75 °C
LP-Polyamide	S, composite	Desalination [c]	96	1000	14 bar, 0.1% NaCl
Polyamide, aromatic, B 9	H, asym.	Du Pont [c]	95	50	28 bar, 0.15% NaCl, pH 4–11, 35 °C
Polyamide, aromatic, B 10	H, asym.	Du Pont [c]	98.5	40	56 bar, 3.5% NaCl, pH 5–9, 35 °C
Polyamide-/hydrazide	S, asym.	Du Pont	99	300	70 bar, 3.5% NaCl, pH 5–9, 35 °C
p-Phenylenediamine/ Trimesoyl chloride, oxidized	F, composite	Film Tec [c]	98	1800	40 bar, 1% NaCl, ≤60 °C, 0.5 ppm Cl_2 (25 °C)
Polyfuran, NS-200	H, composite	FRL	99.5	400	56 bar, 0.2% NaCl
Polyphenylene oxide, sulfonated	composite	General Electric	84	1500	77 bar, 0.1% NaCl, pH 2–13, 54 °C, 1 ppm Cl_2
Piperazine/trimesoyl chloride/isophthaloyl chloride	composite	MRI	50	1700	14 bar, 0.5% NaCl
Polyethylene imine/ Toluylene diisocyanate, NS-100	composite	NSRI	99.4 [e]	900	100 bar, 3.5% NaCl, pH 1–13
Polyfuran NS-200	composite	NSRI	99	1000	70 bar, 3.5% NaCl, pH 2–12, 90 °C
ZrO_2/Polyacrylic acid	dynamically shaped	ORNL	90	7000	70 bar, 0.3% NaCl
Polyfuran	S, composite	Osmonics [c]	99	200	56 bar, pH 0.5–10.5, 75 °C
Glass, phase separation	H [g]	Schott	99.6	100	100 bar, 0.5% NaCl
Co-Polyacrylonitrile [h]	F, T, asym.	Sumitomo Electric Industries [c]	95–98	1000–3000	50–100 bar, 0.6% NaCl, pH 1–10, 45 °C, 0.1 ppm Cl_2
Polybenzimidazolone	asym.	Teijin	99.5 [f]	800	80 bar, 1% NaCl
	S, composite	Teijin [c]	97–99.3	1000	100 bar, 0.7% NaCl, pH 1–12, 60 °C
Piperazine/Polyepiiodohydrin/ Isophthaloyl chloride	S, composite [i]	Toray [c]	99.7	700	40 bar, 0.25% NaCl, pH 4–12, 40 °C
Polyamide TFC-802	composite, PA-100	UOP	99	750	70 bar, 3.5% NaCl
Ethylenediamine/polyepichlorhydrin/Isophthaloyl chloride	composite, PA-300	UOP	99.4	1200	70 bar, 3.5% NaCl, pH 2–12, 55 °C
Polyether-/amide, TFC-803	S, composite	UOP [c]	98.0	600	56 bar, 3.5% NaCl, pH 2–12, 45 °C
Polyether-/urea, TFC-801	S, composite, RC-100	UOP [c]	99.2	600	63 bar, 3.5% NaCl, pH 2–12, 45 °C

[a] The letters and/or numbers after some of the names signify tradenames or type designations. [b] Abbreviations, see Table 8. H = hollow fiber. [c] Commercial product. [d] R (urea) = 88%. [e] R (phenol) = 84%. [f] R (urea) = 72%. [g] In presence of alkyl sulfonates. [h] Cold plasma discharge. Solrox process. [i] Tangential flow.

4.3.2. Preparation of Composite Membranes

As already mentioned, not every polymer can be cast into an asymmetric membrane. Moreover, the thickness of the active layer and the resultant water permeability of the membrane cannot always be optimally controlled. Hence, it was a logical next step to attempt to prepare membranes similar to asymmetric ones by coating an appropriate supporting matrix with a thin homogeneous film. The thin homogeneous film (active layer) could be cast by dipping the support into the corresponding casting solution, by spraying the casting solution onto the porous support, by a cross-linking surface polymerization, or by interfacial cross-linking reactions. The supporting framework must be either refractory to the solvents in the casting solution for the thin-film or must be protected against these solvents by a water soluble intermediate layer. Because of its chemical stability, PS is generally employed to fabricate the fine-porous supporting membrane. When the active layer is prepared by dipping or spraying, penetration of the thin-film casting solution into the pores of the supporting framework is prevented by coating the surface of the porous support with a thin gel-layer (intermediate layer) usually formed by a water-soluble polymer. This gel-layer concomitantly protects the porous support from the solvents of the casting solution. If the polymer molecules of the gel-layer can pass the porous support, the intermediate layer is progressively extracted during operation of the composite membrane. Thus the active layer will finally lie only on the porous support and will have poor mechanical stability. It can be easily delaminated by a sudden drop in the pressure within the membrane module. The mechanical stability of the intermediate layer can be improved by cross-linking the gel. The water content of the cross-linked

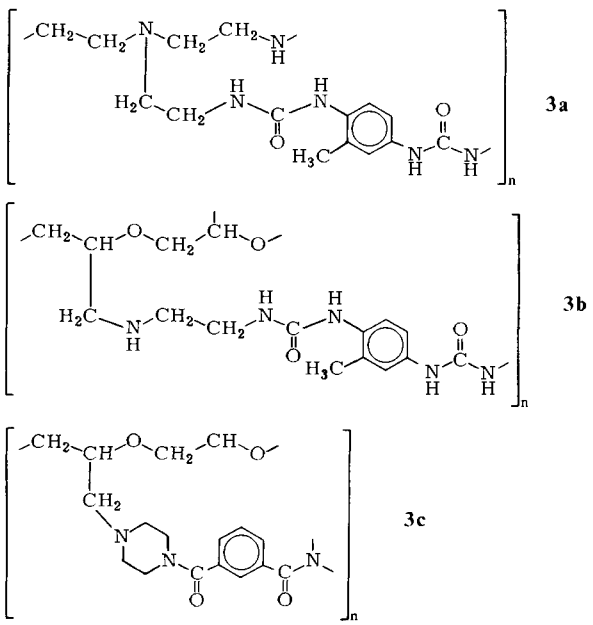


Fig. 27. Structural formulas of basic units of several polymers suitable for the formation of the thin-film of composite membranes. Polyureas **3a** (*e.g.* from polyethylenimine, toluylene diisocyanate [157]), poly(ether/ureas) **3b** (*e.g.* from polyepichlorohydrin (substituted with ethylenediamine), toluylene diisocyanate [158]), and poly(ether/amides) **3c** (*e.g.* from polyepiiodohydrin (substituted with piperazine), isophthalic acid [159]).

intermediate layer should be as high as possible to minimize its hydrodynamic resistance. The active layer can also be attached by covalently cross-linking a gel-layer (*e.g.* amine-modified polyepichlorohydrin) at its surface (interfacial cross-linking). During fabrication the porous support is soaked with the casting solution containing the multifunctional polymer and subsequently brought into contact with a solution of the cross-linking agent (*e.g.* toluylene diisocyanate, isophthaloyl dichloride) in an appropriate organic solvent. In this way an improvement in the adhesion between active layer and supporting framework is obtained. Finally the active layer might be formed from multifunctional amines or acids by direct interfacial polycondensation.

In addition to CA, several other polymers including polyamides, poly(ether/amides), poly(ether/urea), and polybenzimidazolone (PBIL) form suitable barrier films. Figure 27 lists the structural formulas of the monomer units of typical polymers employed in the preparation of thin-films of composite membranes. Table 10b gives an overview of asymmetric and composite membranes.

Improved chemical resistance towards more aggressive process streams and cleaning agents has accelerated the application of synthetic membranes for purposes other than brackish water and seawater desalination. For example, in whey processing, hyperfiltration is gradually supplanting ultrafiltration. In fact, in the USA more hyperfiltration plants were installed for this purpose during 1978—81 than were ultrafiltration plants from 1972—1981. Often, final products may be refined and waste streams purified by using hyperfiltration to concentrate the permeate of ultrafiltration plants. The chemical resistivity necessary for such applications is increasingly being realized with composite membranes containing covalently cross-linked separation layers.

The technical achievements attending hyperfiltration with modules (high packing density) and membranes (high water permeability) have been promptly exploited in gas phase separation processes. Accordingly, homogeneous SD membranes are designed to be preferentially selective towards O_2, CO_2, or He. The properties of synthetic membranes which are predominantly used for gas separation are listed in Table 11 together with permeabilities for selected gases.

Finally, mention should be made of two special composite membranes which have recently been developed for gas separation. The Monsanto Company[136] has successfully developed a composite hollow fiber for gas separation by laminating a void-free non-porous membrane (silicone) onto an asymmetric heteroporous supporting framework. The supporting material was composed of a poylmer (polysulfone) with high selectivity for certain permeant gases (*e.g.* H_2/CO_2) but incapable of being formed into an asymmetric membrane with a pore-free (pin-hole free) skin. The thin-layer (coating) consists of a comparatively permeable but poorly selective polymer. During fabrication, it penetrates into the pin-holes/pores of the active layer of the supporting framework and blocks (*i.e.* prevents convective flow through) these pores. The thickness of this coating varies with depth of penetration. Using such a composite membrane, the theoretically possible separation factor is approached more closely at small ratios of effective surface area of imperfections A_i to effective surface of intact active layer A_a. Monsanto fibers possess a ratio $(A_i/A_a) \simeq 2 \times 10^{-6}$, so that a separation factor of about 33 is calculated for the separation of H_2 from a H_2/CO mixture; this is less than the maximum possible value of 40 for a PS hollow-fiber membrane possessing a completely intact active layer, but is still high enough to make the separation of H_2 from corresponding gas mixtures (*e.g.* H_2/CO) economically feasible.

The second composite membrane concerns SiO_2, which is selectively permeable to O_2; the enrichment of O_2 from air can be achieved by the permeation of air through membranes prepared by sputtering thin films of SiO_2 onto supporting frameworks.

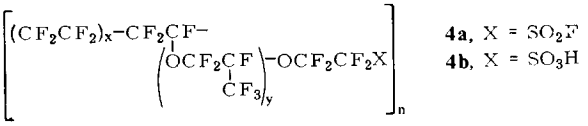
Table 11. Permeabilities $P_s = \Phi_v d/\Delta p$ and separation factors of membranes for gas separation. d = effective membrane thickness, Φ_v = gas flux density, Δp = partial pressure difference across the membrane. P_s is given in [cm³ (STP) cm/(cm² s torr × 10)].

Membrane material/polymer	Permeability $P_s \times 10^{10}$							Separation factor	
	CO_2	O_2	N_2	H_2O	CH_4	He	H_2	O_2/N_2	He/CH_4
Vycor glass (50 Å)	67000	52000	58000	—	80000	150000	200000	0.9	1.9
Polydimethylsiloxane	3200	600	260	40000	590	230	440	2.3	0.4
Silicone/polycarbonate (55/45)	1000	200	90	—	—	—	—	2.2	—
Polyalkylsulfone (C_{16})	260	60	—	—	—	—	—	—	—
Perfluorobutyrylethyl cellulose	230	50	—	—	—	—	—	—	—
Polyisoprene	130	23	10	300	—	36	50	2.3	—
Poly(4-methyl-1-pentene)	93	32	—	—	—	—	—	—	—
Poly(2,6-dimethylphenylene oxide)	75	15	3	4000	—	—	—	5.0	—
Ethyl cellulose	40	10	3	24000	6	31	3	3.3	5.2
Poly(L-leucine/DL-methionine)	40	9	—	—	—	—	—	—	—
High-pressure polyethylene (0.92)	28	6	2	90	—	7	8	3.0	—
Polycarbonate	8	1.5	0.5	1400	3.6	67	14	3.0	18.8
Low-pressure polyethylene (0.96)	4.3	1.1	0.3	15	—	—	—	3.7	—
Poly(vinyl chloride) [a]	3.7	0.6	0.2	590	2	14	13	3.0	7.0
Cellulose acetate	2.4	0.8	0.3	10000	0.3	24	8	2.7	80.0
Teflon FEP	1.7	6	2.1	33	1.4	50	14	2.9	35.7
Polyethylene terephthalate)	0.15	0.03	0.006	175	0.006	1.1	0.6	5.0	183.3
Poly(vinylidene chloride)	0.03	0.005	0.001	1	—	—	0.08	5.0	—
Cellophane	0.006	0.002	0.0005	13000	—	—	—	4.0	—

[a] Contains 30% bis(2-ethylhexyl)phthalate ("dioctyl phthalate", DOP).

4.4. Preparation of Ion-Exchange Membranes

Ion-exchange membranes should contain an as high as possible fixed charge concentration (concentration of ionic groups). Therefore, they have traditionally been prepared from polyelectrolytes rendered water insoluble by cross-linking[137]. Since numerous monographs on ion-exchange membranes are available[138-140], the technique and chemistry of ion-exchange membrane preparation will not be discussed in further detail. Ion-exchange membranes are used for the recovery of salt from seawater as well as for the production of fresh water from brackish water. Original ion-exchange membranes were inadequately chemically resistive for such important applications as in chloride-alkali electrolysis (preparation of NaOH and Cl_2 by electrolysis), or as battery separators, and for separating the cathode and/or anode region from the reaction space in organic electrosyntheses and in fuel cells. The demand for more resistant membranes may be met by polymer materials of higher chemical resistivity such as polystyrene, polyisoprene, polybutadiene, and polytetrafluoroethylene (PTFE). The requisite ionic groups may be attached either to the polymer itself or to the finished film. For example, block copolymers[141] (*e.g.* polystyrene/polyisoprene/polystyrene (SIS-blocks)) to which SO_3H-groups were bound have been successfully prepared. In addition, grafted polymers may be employed[142, 143]. Also *Munari et al.* produced ion-exchange membranes of high thermal and chemical stability by grafting 4-vinylpyridine onto PTFE-films[144]. The Du Pont Company produces a prepolymer for a chemically resistant asymmetric ion-exchange membrane (®Nafion) directly from a perfluorinated monomer. The membrane is formed by extrusion of a perfluorinated polymer containing SO_2F-groups (Fig. 28) and subsequently hydrolyzing the functional groups to SO_3H[145, 146]. There is still a demand for an analogous anion exchange membrane (*e.g.* for electrosyntheses) to complement this chemically stable cation exchange membrane. However, the development of such membranes is rendered difficult owing to the demand for extremely high resistivity towards strong oxidizing agents. Some typical chemically stable ion-exchange membranes are listed in Table 12 together with their most important fields of application.



4a, X = SO_2F
4b, X = SO_3H

Fig. 28. Structural formulas for the basic units of the extrudable perfluoropolymer **4a** used for the preparation of ®Nafion membranes and of the hydrolyzed polymer **4b** with ionic group [145].

5. Future Prospects of Membrane Development

The following separation problems can be elegantly solved with presently available synthetic membranes: Concentration and purification of macromolecular solutions, separation of electrolytes and lower molecular weight non-electrolytes from aqueous solutions, economical fractionation of gas mixtures, and separation of electrode spaces, *e.g.* in electrosyntheses. For these and similar applications a healthy commercial activity has emerged, and its volume will undoubtedly increase in the future (Table 13).

Successful application of membrane technology has generally involved broad-based or categorial separations such as the removal of all polymers or nearly all electrolytes and non-electrolytes from aqueous solutions. Other desirable separations require membranes more selective or more chemically stable than presently available, *e.g.* the fractionation of organic mixtures or separation of selected components from mixtures of electrolytes or non-electrolytes, as in the removal of heavy metal salts from waste

Table 12. Ion-exchange membranes.

Manufacturing process	Manufacturer	Membrane material	Application
"Homogeneous" membranes			
— Copolymerization	Du Pont	Polymer **4b** (Fig. 28) → ®Nafion/asymmetric	Chlor-alkali electrolysis [a] Donnan dialysis [a] Organic synthesis
	Rhône-Poulenc	Poly(acrylonitrile-co-methallyl sulfonate)/symmetric	Hemodialysis [a] Ultrafiltration [a]
— Graft reaction	RAI/Res. Corp.	4-Vinylpyridine on polytetrafluorethylene/symmetric	Pervaporation Fuel cells [a]
	RAI/Res. Corp.	Methacrylic acid on low-pressure polyethylene/symmetric	Battery separators [a]
— Polymer derivation			
(in solution)	Rhône-Poulenc	Polysulfone [b], chlorosulfonated/asymmetric	Hyperfiltration
(in the solid phase)	Asahi Glass Asahi Chem. T. Soda	Polystyrene cross-linked, sulfonated/symmetric	Electrodialysis [a] Electromembrane processes [a]
"Heterogeneous" membranes			
— Domain formation	Ionics	Polystyrenesulfonate latex, cross-linked, quaternated/symmetric	Piezodialysis
— Polyelectrolyte complex	Amicon	Polystyrenesulfonate-poly(vinylbenzyl)-trimethylammonium chloride/asymmetric	Ultrafiltration [a]
— Dynamic formation	Oak Ridge Nat. Lab.	Zirconium hydroxide-polyacrylic acid/asymmetric	Hyperfiltration

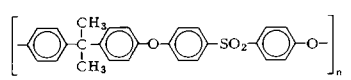
[a] Commercial. [b] Repeat unit of polysulfone: 

Table 13. Membrane films (estimated market volume).

Separation process	Producer	1978 [10^6 DM]	1978 [10^3 m^2]	1983 [10^6 DM]	1983 [10^3 m^2]	Total increase (m^2) [%]
Dialysis	UCC, Hoechst	4	300	3	200	−33 [a]
Battery separation	Grace; RAI, Celanese	200	120000	250	150000	25
Hemodialysis	Membrana, Cordis-Dow, Asahi, Kuraray, Toray, Hoechst	80	20000	150	30000	50
Membrane filtration	Millipore, Pall, Gelman, Sartorius; Cuno; Membrana	370	6000	600	9000	50
Electrodialysis	Ionics, Asahi Chem., Asahi Glass, T. Soda	17	250	30	500	100
Gas separation	Celanese, Cordis-Dow, Monsanto, Dow, UOP (GE)	12	200	20	500	150 [b]
Electrolysis	Du Pont, Asahi Glass, Asahi Chem.	3	5	10	20	300 [c]
Ultrafiltration	Abcor, Romicon, DDS, PCI, Dorr-Oliver, Hoechst	13	70	30	280	300
Hyperfiltration	UOP, Du Pont, Hydranautics, Babcock, Toray, Teijin	10	345	30	1900	450 [d]

[a] Substituted by ultrafiltration. [b] Oxygenation. [c] Chlor-Alkali electrolysis. [d] Calculated as sheet.

waters encountered in the electroplating industry. The chemically stable synthetic membranes presently available (essentially for hyperfiltration) which might be considered for the separation of organic substances all contain water of hydration (and perhaps capillary water). The water of hydration in these membranes is displaced by the organic reagents and the permeability of the membranes decreases continuously with increasing concentration of the organic solvent until $q \simeq 0$[45].

The selectivity of the currently available membranes is insufficient for the solution of specified separation problems since no discrimination occurs between substances of similar size with similar properties (*e.g.* closely related electrolytes or non-electrolytes, different oligomers). Certainly, efforts at developing more discriminating membranes must be mindful of the separative mechanisms in naturally occurring biological membranes, even though these are not yet fully elucidated. In particular, future generations of synthetic membranes might incorporate the hierarchic structure characteristic of living systems, instead of the present format which is unstructured on the molecular level and thus exhibits an irregular (statistical) arrangement of polymer segments.

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COMMUNICATIONS

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The Thermal Conversion of 1,5,9-Triynes into Arenes: [2+2+2]-Cycloadditions or Sigmatropic Rearrangements?**

By *William V. Dower* and *K. Peter C. Vollhardt**

We have shown that 1,5,9-cyclododecatriyne rearranges to hexaradialene under flash pyrolytic conditions[1] through the likely intermediacy of [1,2:3,4:5,6]-tricyclobutenobenzene. However, theoretical work indicates that the thermal [2+2+2]-cycloaddition of three ethynes to benzene is associated, despite being allowed by the Woodward-Hoffmann rules, with a high activation barrier[4] suggesting an alternative: namely, a series of [3.3]-sigmatropic rearrangements involving the 1,5-diyne moieties[5]. We therefore turned to 1,5,9-decatriyne **1**[6], the pyrolysis of which, if it follows the cycloaddition path, should lead to [1,2:3,4]-dicyclobutenobenzene.

Surprisingly, flash or flow pyrolysis of **1** furnishes the linear [1,2:4,5] dicyclobutenobenzene **4**[11] in addition to naphthalene (flash) or the dimethylenecyclobutene **5** (flow). Independent flash pyrolysis of **5** gave **4** and **6** in the same ratio as that obtained from **1**. Compound **4** is stable to the conditions under which it is formed. Pyrolysis of [1,10-D_2]-**1** gave [3,6-D_2]-**4** and [2,10-D_2]-**5**, cleanly.

Schemes 1 and 2 suggest two mechanisms consistent with the observed results, and are distinguishable by a ^{13}C-labeling experiment. The requisite [($^{13}C)_2$]-**1** was prepared from $^{13}C_2H_2$ (90% ^{13}C) by deprotonation, iodination to $^{13}C_2I_2$, coupling with 4-trimethylsilyl-3-butyn-1-ylcopper and protodesilylation. Pyrolysis gave only unscrambled products: [1,2-($^{13}C)_2$]-**4**, [1,4-($^{13}C)_2$]-**5** (Scheme 1), and [9,10-($^{13}C)_2$]-**6** (Scheme 2) as ascertained by high field ^1H- and ^{13}C-NMR experiments, including homo- and heteronuclear decoupling and spectral simulations. In particular, the ^{13}C-NMR absorption for [($^{13}C)_2$]-**4** after ^1H ($\delta = 3.03$) decoupling appears as a triplet at $\delta = 143.3$ ($J = 3.9$ Hz) with the same line-shape as that simulated for the AA'XX' spin system of [1,2-($^{13}C)_2$]-**4** and inconsistent with that calculated for [1,4-($^{13}C)_2$]-**4**. The [1,4-($^{13}C)_2$]-pattern observed for **5** shows that the degenerate rearrangement (**5** ⇌ **9** ⇌ **5**)

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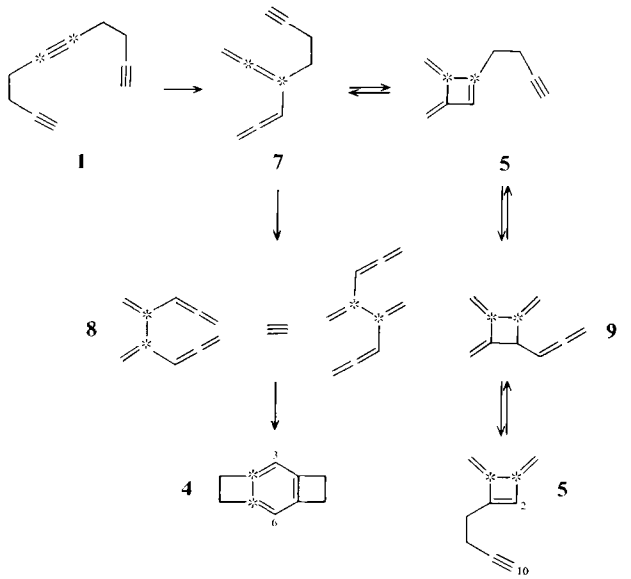
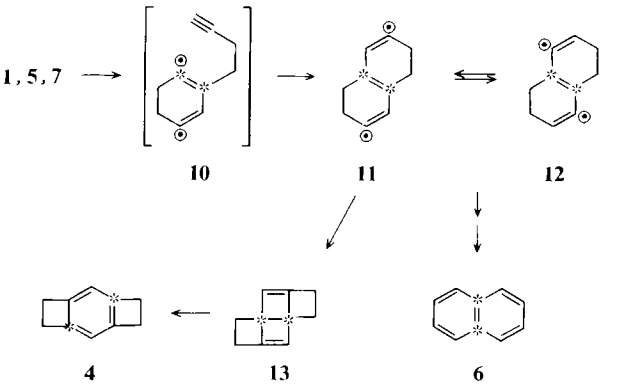


Scheme 1. Possible mechanism of formation of **4** and **5** in the pyrolysis of **1**; * indicates ^{13}C.

postulated in Scheme 1 does not appear to take place. Finally, the distribution of label in **6** indicates the feasibility of Scheme 2 for its formation; intermediate **11** also being derivable from **8**.



Scheme 2. Alternative mechanism of the formation of **4** and suggested path to **6** in the pyrolysis of **1**; * indicates ^{13}C.

Our data provide the first experimental verification of the surprising relative difficulty of effecting intramolecular thermal [2+2+2]-cycloadditions of three alkyne units.

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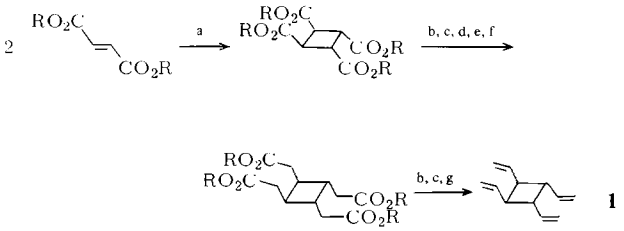
From *cis,trans,cis*-1,2,3,4-Tetravinylcyclobutane to Cyclododecatetraene—Two Consecutive Cope Rearrangements**

By *Klaus Gubernator* and *Rolf Gleiter**

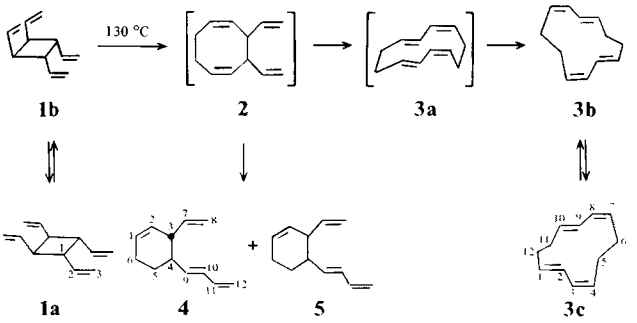
Dedicated to Professor Hermann Schildknecht on the occasion of his 60th birthday

cis,trans,cis-1,2,3,4-Tetravinylcyclobutane **1** [^{1}H-NMR (300 MHz, $CDCl_3$/TMS): $\delta = 5.93$ (dddd, 4H), 5.06 (dd, 4H), 5.04 (dd, 4H), 3.00 (br. d, 4H); ^{13}C-NMR (72.46 MHz, $CDCl_3$/TMS): $\delta = 138.3$, 115.0, 45.3] has been synthesized according to the sequence indicated in Scheme 1.



Scheme 1. *a:* hv, suspension in H_2O, 20 °C; *b:* $LiAlH_4$, tetrahydrofuran (THF), 66 °C; *c:* PBr_3, 120 °C; *d:* KCN, H_2O/C_2H_5OH, 78 °C; *e:* HCl conc. 100 °C; *f:* $CH_3OH/H^{\oplus}$, 60 °C; *g:* KO*t*Bu, THF, 66 °C. R = CH_3.

At temperatures above 120 °C, **1** isomerizes readily and almost quantitatively to a mixture of cyclododeca-1,3,7,9-tetraene **3** and *anti-* and *syn*-4-butadienyl-3-vinyl-1-cyclohexene, **4** and **5**[2], respectively (Scheme 2).



Scheme 2.

The product ratio (63 : 23 : 14) for **3**, **4**, and **5** is essentially independent of reaction temperature and medium (**1** was thermolyzed in the gas phase, as pure liquid or in dimethyl sulfoxide (DMSO) solution). The mixture was separated by preparative gas-chromatography. The isolated pure compounds were stable towards further thermal isomerization at least up to 200 °C.

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We interprete the low temperature of isomerization in terms of a concerted mechanism. It is postulated that **1a** first undergoes a Cope rearrangement[5,6] to 3,4-divinyl-1,5-cyclooctadiene **2** *via* **1b** (see Scheme 2). The intermediate **2** is presumably unstable at the reaction temperature, and undergoes either a second Cope rearrangement to yield **3** or a 1,3-shift[7] to afford the cyclohexene derivatives **4** and **5**[8].

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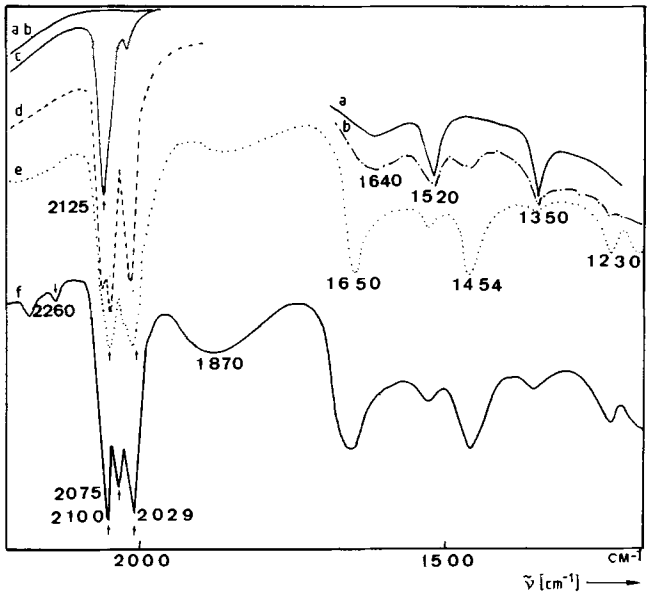


Fig. 1. IR-spectrum of Rh/Al_2O_3 a) after adsorption of $PhNO_2$ **1** (1 torr, 25 °C), b) after heating to 100 °C, c) after CO adsorption (5 torr) at 25 °C, d) after heating to 50 °C, e) to 100 °C, f) to 120 °C.

Mechanistic Aspects of the Carbonylation of Nitrobenzene with Rhodium Catalysts

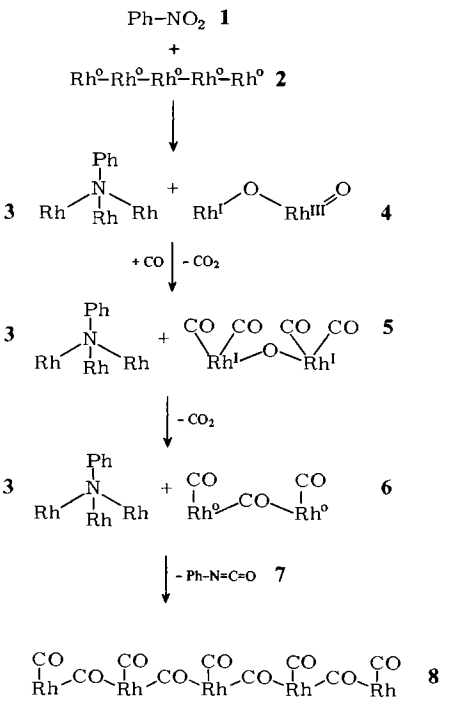
By *B. Elleuch, Y. Ben Taarit, J. M. Basset**, and *J. Kervennal***

Nitro- or dinitroarene compounds in the liquid phase can be carbonylated by rhodium chlorides or rhodium oxides at 120 to 190 °C under CO pressure[1]. Interestingly, the same catalysts as well as the Rh^0 cluster $Rh_6(CO)_{16}$ reduce nitroarenes with CO/H_2O to the corresponding amines[2]. We report here that the carbonylation of nitrobenzene **1** to form phenyl isocyanate **7** can also be performed with metallic rhodium supported on Al_2O_3, and propose a general redox mechanism based on IR studies. This mechanism involves the three common oxidation states of rhodium and the intermediacy of a nitrenerhodium surface complex based on analogues in the coordination chemistry of clusters[3].

Using 461 mg of the Rh^0/Al_2O_3[4] catalyst, nitrobenzene (10 g) in 100 mL of *ortho*-dichlorobenzene in presence of 1 g pyridine is converted into phenyl isocyanate at 240 °C and a CO pressure of 200 bar in 70% yield with 100% conversion after 405 min (1 h initiation time). Among the by-products only azobenzene (0.25%) was identified.

Room temperature adsorption of carefully dried nitrobenzene **1** (1 torr) on the catalyst gives IR bands (Fig. 1) at 1350 (s) and 1520 (s) cm^{-1}, corresponding to the asymmetric and symmetric NO vibrations of adsorbed $Ph-NO_2$, **1**. In addition, a multiplet of weak intensity (1585, 1605, 1620 and 1640 cm^{-1}) corresponding to the CC stretching bands of the phenyl ring occurs. Upon heating the sample to 50 °C or above, the intensity of the ν(NO) bands decreases significantly. Subsequent adsorption of CO (20 torr) gives IR bands at 2125, 2100, and 2029 cm^{-1} corresponding to a $(CO)Rh^{I}$[5] (band at 2125 cm^{-1}) and to a $(CO)_2Rh^{I}$ species. Simultaneously bands which appear at 1650, 1454 and 1230 cm^{-1} indicate the formation of CO_2/carbonates.

Upon increasing the temperature to 120 °C, a band of low intensity is observed at 2262 cm^{-1}, which is typical of adsorbed phenyl isocyanate: the intensity of the bands at 2100 and 2029 cm^{-1} (Rh^{I} species) increases, whereas two bands appear at 2059 and 1860 cm^{-1} corresponding to CO coordinated to metallic rhodium[5]. At 170 °C the ν(CO) bands corresponding to $(CO)Rh^{III}$ and $(CO)_2Rh^{I}$ disap-



Scheme 1.

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pear; only CO coordinated to Rh^0 and gaseous CO_2 can be detected.

Similar behavior is observed if CO is adsorbed on the catalyst prior to the addition of nitrobenzene. Bands corresponding to CO chemisorbed on Rh (2075 (s) and 1870 (br) cm^{-1}) occur. The subsequent adsorption of $PhNO_2$ (1 torr) at room temperature results in a drastic reduction of the intensity of these bands, which are partially replaced by the doublet characteristic of the $(CO)_2Rh^I$ species. Introduction of CO (380 torr) at 100 °C results in the simultaneous formation of Rh^0 coordinated to CO (bands at 2075 and 1870 cm^{-1}) and of phenyl isocyanate (band at 2260 cm^{-1}).

The results can be explained on the basis of the redox mechanism shown in Scheme 1. Nitrobenzene **1** can oxidize Rh^0 **2** to Rh^{III}/Rh^I surface complexes **4**. Simultaneously a phenyl nitrene complex **3** is formed with a structure similar to that already observed in Fe or Ru clusters[3]. The Rh^I/Rh^{III} surface complex **4** can be reduced at 25 °C by CO to $(CO)_2Rh^I$ **5** with simultaneous formation of CO_2. Formation of phenyl isocyanate **7** is observed when **5** is reduced to Rh^0 surface complexes **8**, which would favor CO insertion into the RhN bond. Such insertion is probably the rate-determining step, and at low CO pressure, *i.e.* under non-catalytic conditions, it does not occur.

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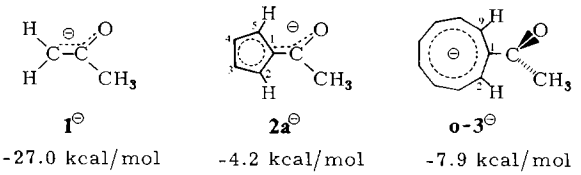
Easy Rotation about the Carbon-Carbon Bond in Lithium Cyclopentadienyl (Ester-)Enolates**

By *Gernot Boche**, *Robert Eiben*, and *Walter Thiel*

The CC "double bond" in (ester-)enolates is conformationally stable referred to the NMR time scale[3d,j]; its double bond character has recently been confirmed by crystal structure data[4]. MNDO calculations are in agreement with both findings[5]: The planar acetone anion $\mathbf{1}^{\ominus}$, *e.g.*, is about 27 kcal/mol more stable than the orthogonal anion $\mathbf{o\text{-}1}^{\ominus}$, rotated through 90° at the CC bond.

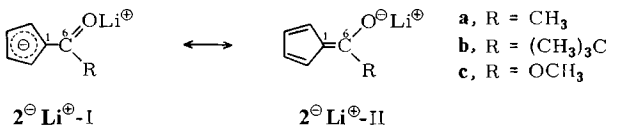
Interestingly, the situation is exactly the reverse in the case of the acetyl-[9]annulene anion $\mathbf{3}^{\ominus}$. The NMR signal of C^{10} ($K^{\oplus}$-salt in [D_8]THF) appears at $\delta = 206.7$[5]. This finding is in no way compatible with a planar enolate structure[3d], but with a non-conjugated methyl ketone.



$\mathbf{1}^{\ominus}$ -27.0 kcal/mol | $\mathbf{2a}^{\ominus}$ -4.2 kcal/mol | $\mathbf{o\text{-}3}^{\ominus}$ -7.9 kcal/mol

Once again, experiment is confirmed by MNDO calculations: the orthogonal anion $\mathbf{o\text{-}3}^{\ominus}$ is about 7.9 kcal/mol more stable than the planar anion $\mathbf{3}^{\ominus}$.

According to MNDO calculations, in the case of the anion of the cyclopentadienyl methyl ketone $\mathbf{2a}^{\ominus}$ the planar conformation is slightly (4.2 kcal/mol) more stable than the orthogonal one, so that (ester-)enolates of this type should be conformationally labile. The ^{1}H- and ^{13}C-NMR spectra (Table 1) of $\mathbf{2a\text{–}c}^{\ominus}\mathbf{Li}^{\oplus}$ confirm this prediction.



$\mathbf{2}^{\ominus}\mathbf{Li}^{\oplus}$-I ⟷ $\mathbf{2}^{\ominus}\mathbf{Li}^{\oplus}$-II

a, R = CH_3
b, R = $(CH_3)_3C$
c, R = OCH_3

Table 1. ^{13}C-NMR spectra (δ values, referred to the solvent [D_8]-tetrahydrofuran (THF)) of $\mathbf{2a\text{–}c}^{\ominus}\mathbf{Li}^{\oplus}$ with 2 equivalents of hexamethylphosphoric triamide (HMPT). Signal indices: without index = sharp; sb = slightly broadened; b = broadened; hb = highly broadened.

	T[°C]	C^1	$C^{2,5}$		$C^{3,4}$		C^6
$\mathbf{2a}^{\ominus}\mathbf{Li}^{\oplus}$	27	124.6	117.7	116.0	114.0	114.0	183.3
$\mathbf{2b}^{\ominus}\mathbf{Li}^{\oplus}$	27	120.9	115.6		112.9		194.1
	−21	120.7	114.8 (hb)		111.0 (b)		193.7
	−34	120.7	115.6 (b)	114.0 (b)	111.4 (b)	110.4 (b)	193.6
	−62	120.6	115.4 (sb)	113.8 (sb)	111.1 (sb)	110.3 (sb)	193.5
$\mathbf{2c}^{\ominus}\mathbf{Li}^{\oplus}$	27	107.8	113.4		110.0		168.7
	−20	107.7	113.7 (hb)	113.2 (hb)	111.1 (hb)		168.7
	−40	107.8	113.9 (sb)	113.0 (sb)	111.5 (sb)	111.0 (sb)	168.5

Methyl enolate $\mathbf{2a}^{\ominus}\mathbf{Li}^{\oplus}$: From −60 to 55 °C the same spectra are obtained as at 27 °C. The constantly sharp and different signals of C^2 and C^5 allow only one interpretation: The rotation about the C^1C^5 bond is slow referred to the NMR time scale.

tert-Butyl enolate $\mathbf{2b}^{\ominus}\mathbf{Li}^{\oplus}$: At 27 °C, the atom pairs C^2 and C^5 as well as C^3 and C^4 each give *one* sharp signal; at −21 °C these signals are broadened, and at −34 °C each are split into two lines, which, at −62 °C, are only slightly broadened: C^1 and C^6, on the other hand, always show sharp signals. This spectral behavior is compatible only with a dynamic process due to rotation about the C^1C^6 bond. Other likely causes for such a behavior, namely protonation-deprotonation or aldol-like reactions with any *tert*-butylcyclopentadienyl ketone that may be present, would involve all C atoms participating in the dynamic process and, moreover, should also occur in the case of $\mathbf{2a}^{\ominus}\mathbf{Li}^{\oplus}$. From the coalescence temperature of the signals of C^2 and C^5 the values $k = 96.5\ s^{-1}$ and $\Delta G^{\neq} = 12.4 \pm 0.2$ kcal/mol are obtained for the rotation at 21 ± 4 °C. Since the spectra of $\mathbf{2b}^{\ominus}\mathbf{Li}^{\oplus}$ in [D_8]THF *without* HMPT are almost the same, aggregation and ion-pair effects are, remarkably, of no decisive importance in the rotation about the C^1C^6 bond in $\mathbf{2b}^{\ominus}\mathbf{Li}^{\oplus}$[14c]. The difference in behavior of $\mathbf{2a}^{\ominus}\mathbf{Li}^{\oplus}$ and $\mathbf{2b}^{\ominus}\mathbf{Li}^{\oplus}$ stems from the steric hindrance in the ground state of $\mathbf{2b}^{\ominus}\mathbf{Li}^{\oplus}$. The "transition states" **o-**

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2a$^{\ominus}$**Li**$^{\oplus}$ and **o-2b**$^{\ominus}$**Li**$^{\oplus}$ should have comparable energies[14c].

Ester enolate **2c**$^{\ominus}$**Li**$^{\oplus}$: The same applies for **2c**$^{\ominus}$**Li**$^{\oplus}$ as for **2b**$^{\ominus}$**Li**$^{\oplus}$ (Table 1); the influence of HMPT is likewise minimal. At -14 ± 4 °C $k=51.4$ s^{-1}, $\Delta G^{\neq}=13.0\pm0.2$ kcal/mol. What distinguishes **2c**$^{\ominus}$**Li**$^{\oplus}$ from **2a**$^{\ominus}$**Li**$^{\oplus}$? Since the steric relations ought to be similar, it must be the weaker acceptor properties of the methoxycarbonyl group, which, in the case of the ester enolate, gives relatively greater importance to the resonance structure **2c**$^{\ominus}$**Li**$^{\oplus}$-I, corresponding to easier rotation.

The signals of the "carbonyl" C-atoms (C^6) of **2a,b**$^{\ominus}$**Li**$^{\oplus}$ lie close to those in the corresponding ketones ($\Delta\delta=13.0$ and 7.2 ppm, respectively; silyl enol ether: $\Delta\delta=21.2$ and 22.4 ppm, respectively). In contrast, in the case of "normal" enolates[3d] the values resemble rather those of the silyl enol ether. This confirms the stability of the planar conformation of "normal" enolates and is thus in accord with the ease of rotation about the CC "double bond" observed in **2b,c**$^{\ominus}$**Li**$^{\oplus}$ and predicted by MNDO calculations[19]. This effect was hitherto not known in the case of (ester-) enolates.

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Solid-State ^{13}C-NMR Spectra of Cyclotriprolines**

By *Horst Kessler**, *Wolfgang Bermel*, and *Hans Förster*

Although thanks to the cross polarization magic angle spinning technique (CP-MAS) high resolution ^{13}C-NMR spectra of compounds in the solid-state can almost be obtained on a routine basis today, there are only a few compounds for which X-ray structural analyses *and* solid-state NMR spectra have been obtained[1]. Studies of this type, however, must be carried out in order to understand the influence of intermolecular interactions on chemical shifts in ^{13}C-NMR spectra in the solid-state.

Both X-ray structural analysis[2], and ^{1}H- and ^{13}C-NMR studies in solution[3] have been carried out on the two cyclotriprolines *cyclo*[L-Pro_3] **1** and *cyclo*[L-Pro_2-D-Pro] **2**. In the crystal each compound exists in two independent molecular forms, which also differ from each other in the conformations of the proline ring. In consequence, six signals for each type of carbon atom (CO, C_α, C_β, C_γ, C_δ) are expected for the solid-state ^{13}C-NMR spectrum of **1**, which has C_3 symmetry in solution. However, this is not observed. Only the signals for CO exhibit two additional signals. The carbon atoms of the ring show only relatively broad singlets with a hint of splittings (Fig. 1, top). Even in solution the unsymmetric cyclotriproline **2** exhibits $3\times5=15$ signals[4]. Every signal should be doubled-up in the crystal. The ^{13}C-CP-MAS spectrum (Fig. 1, bottom)

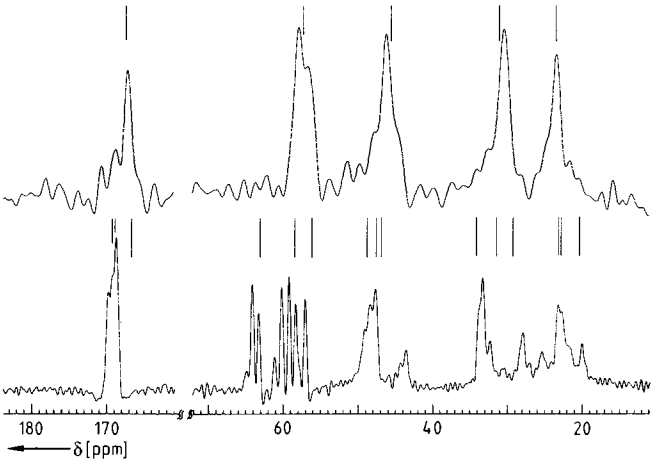

Fig. 1. Solid-state ^{13}C-NMR-CP-MAS spectra (300 MHz, RT) of *cyclo*[L-Pro_3] **1** (top) and *cyclo*[L-Pro_2-D-Pro] **2** (bottom). For purposes of comparison the position of the signals in the solution spectrum ($CDCl_3$) is shown in the middle. The signals are assigned for left to right in the sequence CO, C_α, C_δ, C_β, and C_γ.

clearly shows this effect for the C_α atoms; we do not interpret the splittings for these atoms as arising from ^{14}N quadrupolar coupling[5], since at the field strength used (300 MHz (^1H) = 7.05 T) the splittings should be smaller. Moreover, more asymmetric bands of greater line width would be expected. In the C_δ ($\delta=40-50$), and C_β and C_γ ($\delta=20-35$) regions also, an increased number of lines is indicated because of splittings and anomalous signal intensities. Conspicuous is the difference between the solid-state and solution spectra in the carbonyl region. In solution, the three CO signals (in $CDCl_3$: $\delta=166.8$, 168.9, 169.3) can be readily resolved, whereas in the solid-state, instead of the expected six signals, the splitting of the signals between $\delta=168$ and 170 is only hinted at. In the solid-state spectrum the lines, which compared to those of the solution spectrum are broader, nearly coalesce. A similar effect is found for the C_β signals (in $CDCl_3$: $\delta=29.1$, 31.3, 34.0).

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[**] Peptide conformations, Part 16. This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft. Part 15: H. Kessler, W. Hehlein, R. Schuck, *J. Am. Chem. Soc.*, in press.

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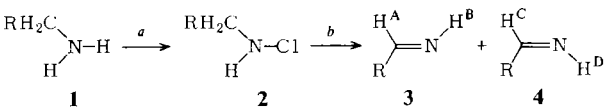
Vacuum Dynamic Gas Phase/Solid-Phase Reactions: *N*-Chlorination of Primary Amines and α-Elimination of the Resulting Chloramines; Synthesis of Reactive (*E*)- and (*Z*)-Aldimines

By *Jean-Claude Guillemin* and *Jean-Marc Denis**

The (*E*)- and (*Z*)-aldimines **3** and **4** are intermediates in chemical and enzymatic oxidations of primary amines, as well as in the dehydration of aldehyde-ammonia adducts. Several of them have been detected in the pyrolysis decomposition products of alkylamines, cyclic aldimine trimers, and alkylazides, but information concerning their stereochemistry is scarce and conflicting. Attempts to isolate and characterize both the (*E*)- and (*Z*)-isomers of this class of compounds as stable free bases have so far failed.

Reactive species have been recently synthesized by vacuum dynamic gas/solid phase reactions[1]. We report here the direct synthesis of the reactive aldimines **3a—3f** and **4a—4f** by a "one-pot" multistep sequence carried out in a single vacuum line: *N*-chlorination of the primary amines **1** on solid *N*-chlorosuccinimide (NCS) is followed by an α-elimination reaction of the resulting N-chloramines **2**[7] over solid potassium *tert*-butoxide[13] (Scheme 1).



1 **2** **3** **4**

a, R = CH_3; **b**, R = C_2H_5; **c**, R = C_3H_7; **d**, R = $CH{=}CH_2$;
e, R = $CH_2{-}CH{=}CH_2$; **f**, R = $=(CH_2)_2{-}CH{=}CH_2$

Scheme 1. Synthesis of **3a—3f** and **4a—4f**. *a:* solid NCS, RT, 10^{-1} torr; *b:* solid KO*t*Bu, 55 °C, 10^{-1} torr. In **3e** and **4e** R = CH=CH—CH_3, the CC double bond is (*E*)-configurated.

Unsaturated *N*-chloramines **2d—2f** are unstable and cannot be revaporized. For this reason, vacuum chlorination of amines **1** on solid NCS and elimination of the resulting chloramines **2** on solid potassium *tert*-butoxide[13] were carried out successively in a single vacuum line, leading in good yields to a mixture of the reactive (*E*)- and (*Z*)-aldimines **3** and **4**, which were characterized by their low temperature IR (−196 °C), ^{1}H-, and ^{13}C-NMR spectra (−100 °C) (Table 2). No (*E*)/(*Z*)-isomerization occurs in solution at low temperature. Stereoselectivity was observed, the main product in all cases being the (*E*)-isomer (72%), even though—as was found in the case of **3a**[14]—it is the less thermodynamically stable isomer. Proof of the constitution of the imines is provided by the low-temperature formation of *s*-triazines. In absence of solvent, the imines polymerize at *ca.* −120 °C.

Table 2. (*E*)- and (*Z*)-aldimines **3** and **4** from **1** [a].

	Yield		^{1}H-NMR [c]		IR [d]
	3+4 [%] [b]	**3/4**	$^3J_{H^AH^B}$ [Hz]	$^3J_{H^CH^D}$ [Hz]	$\tilde{\nu}$(C=N) [cm^{-1}]
a	89	2.3/1	15.9	25.3	1642
b	85	2.6/1	16.1	23.0	1640
c	55	3.0/1	15.4	24.4	1640
d	30 [e]	2.7/1	15.9	25.1	1638
e [f]	53	2.3/1	15.5	27.0	1639
f	52	2.3/1	15.6	24.4	1640

[a] For methanimine the following values are known: ^{1}H-NMR: $^3J_{cis} = 17.0$ Hz, $^3J_{trans} = 25.0$ Hz; IR: $\tilde{\nu}$(C=N) = 1639 cm^{-1} [1c]. [b] Yields calculated by ^{1}H-NMR using *t*BuOH as internal standard. [c] 10% solution in $CD_2Cl_2 + CFCl_3$ at −100 °C with TMS as internal standard. [d] NaCl window cooled with liquid nitrogen. [e] Together with 45% of **8**. [f] Only the 1-propenyl derivatives are formed by base-catalyzed isomerization.

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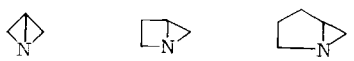
The main (if not the only) pathway for the transformation of **2** to **3/4**, no evidence of a typical nitrene process was



8 **9** **10**

found and, specifically, no intramolecular cyclization *via* C—H insertion was observed. 1-Azabicyclo[1.1.0]butane **8**[18] was the main product in the elimination of **2d**, but no bicyclic compounds **9** or **10** were detected in the elimination of **2e** and **2f**, respectively.

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[7] *N*-Chloramines **2** were characterized by their low temperature ^{1}H-NMR, room temperature-IR (CCl_4), and mass spectra.
[13] In a previous paper [1a], silica- or alumina-supported KO*t*Bu was used to minimize sublimation of the base (temperature > 80 °C). When HCl-elimination of primary chloramines occurs at lower temperature (≤ 55 °C), solid KO*t*Bu can be used directly.
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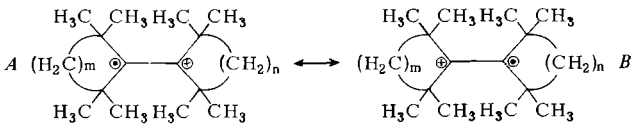
Is the Unpaired Electron in Radical Cations of Sterically Hindered Alkenes Localized or Delocalized?**

By *Horst Eierdanz* and *Armin Berndt**

An electron exchange between the *localized* structures *A* and *B* was recently postulated[1] for the sterically hindered radical cations **1—3**; it was suggested that the frequency of this process strongly decreases with increasing steric hindrance, and that **3** behaves like an alkyl radical ESR spectroscopically.

By labeling an sp^2 C atom of **3** with ^{13}C we have now been able to demonstrate that the unpaired electron in **3**— and, hence, also in the less hindered radical cations **1** and **2**—is *delocalized*.



1, m = n = 1;
2, m = 1, n = 2;
3, m = n = 2

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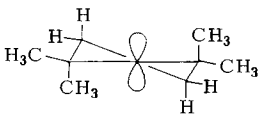
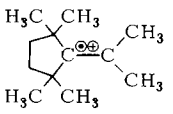
The *localized* structure *A* or *B* for **3** was derived from the result that only 12 of the total 24 methyl protons and only four of the total eight methylene protons lead to a splitting of the ESR spectrum. From this is was concluded that the unpaired electron couples with the protons "in *only one* cyclopentylidene-half"[1]. The result is, however, also consistent with a *delocalized* structure $A \leftrightarrow B$, if one assumes that the cyclopentylidene rings occur in conformation *C*[2], which is fixed on the ESR time scale, with a total of four axial and four equatorial methyl groups and methylene protons, of which only one of each type couple with the unpaired electron.

This alternative appears at first to be less attractive, since it must be combined with a high inversion barrier[6b] and infinitesimally small coupling constants for half of the protons[6c]. We obtained evidence, however, that this could be the case by studying the radical cations **4** and **5** ($a^{H}_{\beta\text{-}CH_3} = 1.43$ and 1.38 mT, respectively), which at −90 °C exhibit ESR coupling constants of 0.23 and 0.25 mT, respectively (**3**: 0.203 mT[1]) for *only six* of the twelve γ-methyl protons.



C



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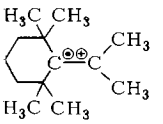
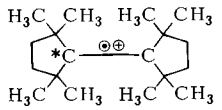
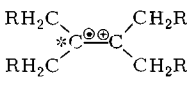


5

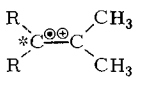
The alternatives should be clearly distinguishable from one another in the ^{13}C labeled radical **3***: *two* coupling constants having values similar to those of a tertiary alkyl radical (*ca.* 4.5 mT for the radical center and *ca.* 1.2 mT for the neighboring sp^2-C atom with the positive charge) are cted for the localized structure. In contrast, for the delocalized structure only *one* coupling constant is expected which—as in the delocalized radical cations **6***[3] ($a^{C} = 0.85$ mT) and **7*** (at −40 °C: $a^{H} = 1.48$ mT (6H), $a^{H} = 0.065$ mT (18H), $a^{C} = 0.86$ mT, $g = 2.0027$)—should be *ca.* 0.9 mT.



3*



6*



7*

* = ^{13}C-labeled; R = $C(CH_3)_3$

We obtained cyclopentanone with a ^{13}C labeled carbonyl group in 38% yield by allowing the dimagnesium compound of 1,4-dibromobutane[4] to react with $^{13}CO_2$ (24% ^{13}C) in tetrahydrofuran; **3*** was then prepared as described[5].

The ESR spectrum of **3*** can be simulated using the proton coupling constants mentioned in [1] and *one* ^{13}C coupling constant of 0.88 mT [6]; this proves the delocalized electronic structure $A \leftrightarrow B$ for **3**. The less hindered radicals **1** and **2** should have the same electronic structure. The temperature-dependent line-width effects observed for **2**[1] may not arise from electron exchange but from ring inversion of the cyclopentyl ring, which because of the smaller steric hindrance takes place with a higher frequency than in **3**.

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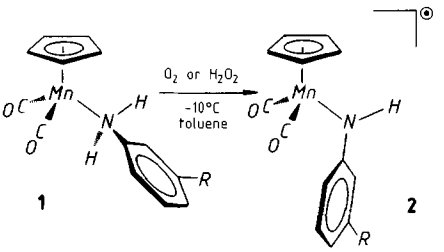
[6] Furthermore, in **3** and **3*** we observed a ^{13}C coupling constant for four C atoms in natural abundance with $a^{C} = 0.98$ mT, which we assign to the C atoms of the four axial methyl groups. b) The barrier must be higher than *ca.* 8 kcal/mol, since even at +30 °C the width of the hyperfine lines is only 0.007 mT, and hence no indication of an inversion process is obvious (F. Gerson, personal communication). c) This is apparent both from the narrow ESR line width and from the fact that no signals near the frequency of the free proton are observed in the ENDOR spectrum (F. Gerson, personal communication).

$C_5H_5(CO)_2Mn$(*m*-Toluidinyl), An Isolable Aminyl Complex**

By *Dieter Sellmann**, *Jürgen Müller*, and *Peter Hofmann*

Aminyl radicals, $^{\odot}NHR$, usually cannot be isolated because of their high reactivity; they are assumed to be intermediates in oxidation reactions catalyzed by metal enzymes (*e.g.* peroxidase) and in the photolysis or radiolysis of amines[1]. During our investigation of redox reactions of metal complexes with nitrogen ligands we succeeded in trapping and stabilizing the toluidinyl radical, which is not isolable as such, in the paramagnetic manganese complex **2**, R = CH_3; to our knowledge this compound represents the first aminyl complex.



1 **2**

If the *m*-toluidine complex **1** (ν_{CO}: 1922, 1847 cm^{-1}, obtained from $C_5H_5(CO)_2Mn(THF)$ and *m*-$CH_3C_6H_4NH_2$ by standard procedures[2a]) is oxidized with air or H_2O_2, the red-brown toluene solution immediately turns deep blue and two new ν_{CO}-bands can be observed IR-spectroscopically at 1968 and 1920 cm^{-1}. After concentration of the solution and addition of hexane the blue-black *m*-toluidinyl complex **2** crystallizes at −78 °C as analytically pure microcrystals[2b].

In the solid state **2** is stable at room temperature for several hours; it is characterized by one ν_{NH}- and two ν_{CO}-bands at 3340 and 1959/1902 cm^{-1} (KBr), by its mass-

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[**] Reactions of Complexed Ligands, Part 34. This work was supported by the Fonds der Chemischen Industrie and the Dr. Otto Röhm-Gedächtnisstiftung. We are indebted to Dr. G. Grampp for recording the ESR spectra.—Part 33: D. Sellmann, H. E. Jonk, H. R. Pfeil, G. Huttner, J. von Seyerl, *J. Organomet. Chem.* 191 (1980) 171.

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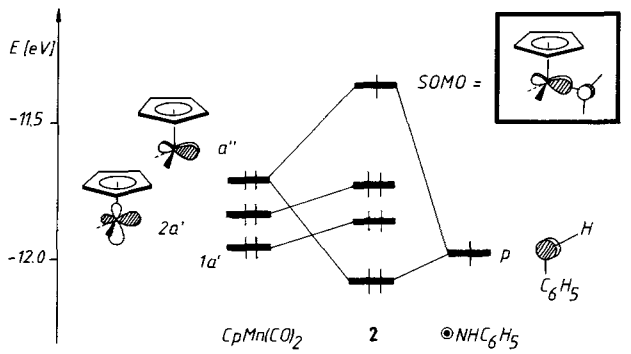
spectrum (FD and EI; M^+ at $m/z = 282$, 70% rel. int.), and by an absorption at $\lambda = 660$ nm ($\varepsilon_{max} = 4060$ L/cm mol). The paramagnetism expected from the empirical formula is confirmed by a magnetic moment of 2.2 μ_B (Gouy-balance). From the observed sextet in the ESR-spectrum (acetone solution, -30 °C) with $a^{55}_{Mn} = 5.0$ mT one can conclude, that the unpaired electron is localized in a molecular orbital with predominant metal character; no coupling to N or H nuclei is observed.

Aminyl complexes like **2** are isoelectronic to radical anions of carbene complexes; according to ESR measurements the unpaired electron of the latter is localized mainly at the carbene ligand[3]. The different electronic structure of both species is revealed by MO calculations[4] on $C_5H_5(CO)_2MnNHC_6H_5$ (**2**, R = H). The geometry of **2** in the structural formula with planar coordination of the N atom is found to be the conformation of lowest energy. The rotational barriers around the N-phenyl and especially the Mn—N bond, however, are very low. The unpaired electron is located in an energetically stable molecular orbital (energy difference to the LUMO *ca.* 3 eV) independent of the conformation; this MO is localized 70—80% in the $C_5H_5(CO)_2Mn$-part of the molecule. As shown in Scheme 1, the SOMO is to be regarded as the antibonding linear combination of the $C_5H_5(CO)_2Mn$-HOMO (a″) with the nitrogen p-orbital. At an orthogonal position of the $^{\odot}$NHR ligand the $C_5H_5(CO)_2Mn$ fragment orbital 2a′, nearly degenerate with a″, takes over the role of the latter; for positions in between an appropriate linear combination of both MO's is utilized.



Scheme 1. Simplified interaction diagram for metal complex fragment [5] and aminyl radical.

Thus, for aminyl complexes like **2** the higher electronegativity of the nitrogen-center compared to carbon causes localization of two electrons as a lone pair at N (lowest level in Scheme 1) and of the unpaired electron in the d-shell of the metal, in accordance with the rules of the perturbation theory. On the other hand, the d-shell of carbene complex radical anions (p in Scheme 1 lies at substantially higher orbital energy) remains fully occupied and the radical electron resides on the ligand-system in the original LUMO of the neutral carbene complex. In a one-electron scheme the lowest absorption in the electronic spectrum of **2** corresponds to a transition from the d-shell to the SOMO with π^*_{dp}-character, analogous to the $d \rightarrow \pi^*_{NN}$-transition in $[C_5H_5(CO)_2Mn]_2N_2H_2$.

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[2] a) Cf. also D. Sellmann, W. Weiss, *J. Organomet. Chem. 160* (1978) 183; b) *Procedure:* To a stirred solution of 940 mg (3.3 mmol) **1** in 100 mL toluene at -10 °C are added 4 mL of 30% H_2O_2 (≙38 mmol). The solution immediately turns dark blue and, after *ca.* 5 min, is concentrated to 5 mL. After addition of 100 mL of hexane the solution is cooled to -25 °C and filtered. At -78 °C, 258 mg (27%) of blackish-blue **2** crystallizes within 24 h; the compound is analytically pure after washing with hexane.—For oxidizing with O_2, air is passed through a solution of **1** in toluene at -10 °C for 2—3 h until the ν_{CO}-bands of **1** have disappeared. Work-up as above.

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Cluster Synthesis by Exchange of Bridge-Forming Carboxylate Ligands**

By *Helmut Werner** and *Peter Thometzek*

Procedures for the directed synthesis of metal clusters from smaller mono- and binuclear synthons are still sparsely documented[1]. We have recently shown that dipalladium complexes $(\mu\text{-X})(\mu\text{-Y})Pd_2(PR_3)_2$ are obtainable by "[1 + 1]-addition" of a Pd^0- and a Pd^{II}-compound, and that a large variety of bridge ligands, such as C_5H_5, 2-RC_3H_4, Cl, SR, RCO_2 *etc.*, have proven suitable in such additions[2].

According to MO calculations by *Hofmann*[3] metal complex anions $[L_nM]^-$ should also be capable of bridge formation with the fragment $(\mu\text{-Y})Pd_2(PH_3)_2^+$ if they contain two donor orbitals of symmetry a_1 and b_2 which can overlap with the corresponding acceptor orbitals of the Pd_2-moiety. This prerequisite is fulfilled, *e.g.*, in the case of the carbonyl(cyclopentadienyl)metalates $[C_5H_5(CO)_nM]^-$ (M = Ni, Fe, Cr; $n = 1, 2, 3$)[3]. In preliminary experiments we were able to demonstrate that, as predicted, the complex $(C_5H_5)(t\text{BuCO}_2)Pd_2(P\text{i}Pr_3)_2$ **1** does in fact react with $[C_5H_5(CO)_3Cr]Na$ and $[C_5H_5(CO)_3Mo]Na$, and that replacement of the carboxylate by the metalate takes place[2d].

This exchange process is, however, not restricted to the anions $[C_5H_5(CO)_3M]^-$. Reaction of **1** and $[(CO)_4Co]Na$ (toluene, 25 °C, 24 h) affords the Pd_2Co-cluster **2** which forms dark violet, permanganate-like crystals (yield 78%). We assume that in **2** the cyclopentadienyl ring and the $(CO)_4Co$-moiety are symmetrically coordinated to the Pd—Pd bond. The ^{1}H-NMR spectrum (C_6D_6) shows, aside from the signals of the $i\text{Pr}_3$P-ligand, a 1 : 2 : 1 triplet for the C_5H_5 protons [$\delta = 5.74$ (t, $J_{PH} = 1.9$ Hz)], whereas the ^{31}P-NMR spectrum (C_6D_6) shows a singlet for the two equivalent phosphorus atoms [$\delta = 37.78$ (s)]. The IR spectrum (KBr) shows bands for both terminal [2029, 2011, 1990, 1961 cm^{-1}] as well as bridging CO groups [1858 cm^{-1}].

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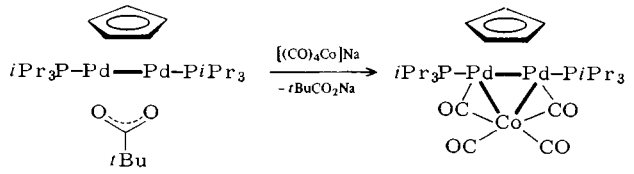
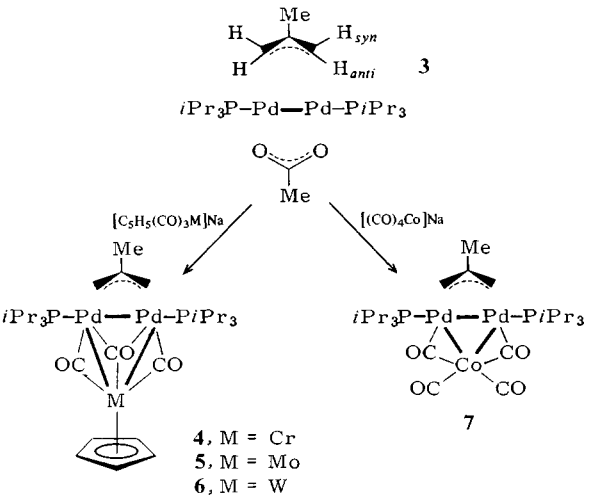


1 2

Reaction of **1** with $[(CO)_5Mn]Na$ does not lead to the expected Pd_2Mn-cluster; instead, $C_5H_5Mn(CO)_3$ is formed, so presumably attack of the metalate at the bridging cyclopentadienyl ring takes place.

The carboxylate bridge in compound **3** is also replacable by one of the complex anions $[C_5H_5(CO)_3M]^-$ (M = Cr, Mo, W) and $[(CO)_4Co]^-$. In toluene (25 °C, 24 h) the Pd_2Cr- and Pd_2Co-clusters **4** and **7** are formed almost quantitatively. With a molar ratio of **3** : $[C_5H_5(CO)_3M]^-$ of *ca.* 1 : 1 the yields of **5** and **6** are considerably lower because the hydrido compounds $C_5H_5(CO)_3MH$ (M = Mo, W) are formed as well as the trinuclear complex. These can be separated by column chromatography on silica gel with pentane and toluene as eluent. In each case, the ^1H-NMR spectra (C_6D_6) show, in addition to the signals for the cyclopentadienyl and phosphane ligands, a virtual triplet for the H_{syn}-, a broadened singlet for the H_{anti}-, and a virtual triplet for the 2-CH_3-allyl protons. After ^{31}P-decoupling the virtual triplets transform into a singlets. The IR spectra (KBr) of **4**—**6** each show three ν(CO) bands at *ca.* 1840, 1770, and 1725 cm^{-1} which are assigned to the doubly and triply bridging CO ligands. The IR spectra of **2** and **7** are very similar. The empirical formulas of the compounds **4**—**7** are confirmed by elemental analyses and field desorption mass spectra.



4, M = Cr
5, M = Mo
6, M = W

The bridge-forming property of the $[(C_5H_5(CO)_3M]$- and $(CO)_4Co$-moieties in Pd^{II} complexes has recently been described in the literature[4]; in these cases, however, owing to the oxidation number II of the palladium no Pd—Pd bonds, and thus no clusters, are strictly present[5].

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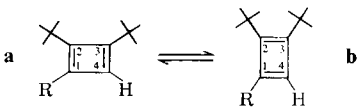
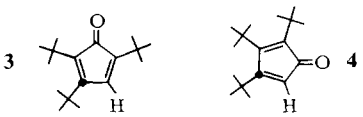
Cyclobutadiene: Mesomerism or Valence Isomerism?**

By *Günther Maier**, *Hans-Otto Kalinowski*, and *Klaus Euler*

Benzene and cyclobutadiene are worlds apart: in benzene the π electrons are completely delocalized and the two Kekulé structures merely serve to describe the mesomerically stabilized molecule. In contrast, in cyclobutadiene[1] both forms **a** and **b**—on condition of a rectangular singlet ground state—are capable of existing in a dynamic equilibrium of valence isomers. We report here the first direct spectroscopic evidence[2] for this postulate. Since the



1, R = t-C_4H_9; **2**, R = t-C_4D_9



equilibrium **1a** ⇌ **1b** could not be frozen (even at −185 °C the olefinic C atoms C-1 and C-3 exhibit a single sharp signal)[3a], we used the isotopic perturbation method of *Saunders*[4], *i.e.* we studied the degenerate equilibrium **2a** ⇌ **2b**.

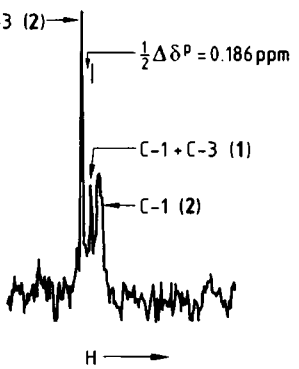


Fig. 1. Part (C-1 + C-3) of the 25.2 MHz ^{13}C-NMR spectrum of a mixture of **1** and **2** (1 : 9) in deuterated diethyl ether at −82 °C.

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[**] Small Rings, Part 45. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 44: G. Maier, K.-A. Schneider, K.-D. Malsch, H. Irngartinger, A. Lenz, *Angew. Chem. 94* (1982) 446; *Angew. Chem. Int. Ed. Engl. 21* (1982) 437; *Angew. Chem. Suppl. 1982*, 1072.

2 can be prepared from di-*tert*-butylacetylene and (nonadeuterio-*tert*-butyl)maleic acid anhydride[3]. The ^{13}C-NMR spectrum of a mixture of **1** and **2** differs from that of **1** in that in **2** the signal for C-1/C-3 (**1**: $\delta = 151$) is split. Apparently the deuterium substitution perturbs the equilibrium **2a** $\rightleftharpoons$ **2b** and, in consequence, C-1 and C-3 can be observed separately. Not only C-3, but also C-1 shows practically no intrinsic isotope effect. The high-field signal is broadened by vicinal ^{13}C-D coupling, whereas the low-field signal exhibits no fine structure. We have, therefore, ascribed the splitting to a doubling of the separation between the signal for C-1/C-3 in **1** and the low-field signal for C-3 in **2**. The splitting $\Delta\delta^p$ (p $\triangleq$ perturbation) thus obtained is temperature dependent and increases from 0.30 ppm at $-62\,^\circ C$ to 0.45 ppm at $-96\,^\circ C$ and is 0.37 ppm at $-82\,^\circ C$ (Fig. 1). The temperature dependence of $\Delta\delta^p$ clearly suggests a dynamic equilibrium **2a** $\rightleftharpoons$ **2b** and not a delocalized π system[4b].

Since the chemical shifts for C-1 and C-3 in **2** cannot be determined in the "frozen" state, suitable models must be used to determine the splitting to be expected in the static molecule ($\Delta\delta^{st}$). Neighboring effects as in **2a** and **2b** (coupling of C-1 with C-2 and C-4 *via* a single and double bond; additional *tert*-butyl group at C-3) also occur in the cyclopentadienones[5] **3** and **4**. In this way a value of 8.5 ppm is estimated for $\Delta\delta^{st}$.

$$K = \frac{\Delta\delta^{st} + \Delta\delta^{p}}{\Delta\delta^{st} - \Delta\delta^{p}} \qquad \text{(a)}$$

Using eq. (a)[4] the equilibrium constant $K = 1.0915$ is obtained; this corresponds to a ratio of 52 : 48 for the valence isomers; the temperature dependence of K gives the ground state values $\Delta H^0 = -354$ (± 46) J mol^{-1} and $\Delta S^0 = -1.1$ (± 0.3) J mol^{-1} K^{-1}.

Since the high-field signal in **2**, on the basis of the ^{13}C-D coupling, is assigned to C-1, the equilibrium must be displaced in favor of **2a**. The high-field shift of C-1 is reasonable, since comparison with the cyclopentadienones indicates that in the isomer **3** with substitution pattern analogous to **2a** (double bond to the *tert*-butylated neighbor) the labeled C atom appears at higher field than the corresponding atom in **4**. The preference for **2a** depends on the "steric isotope effect"[4c]: the t-C_4D_9 is smaller than the t-C_4H_9 group and results in a greater reduction in energy in **2a** than in **2b**.

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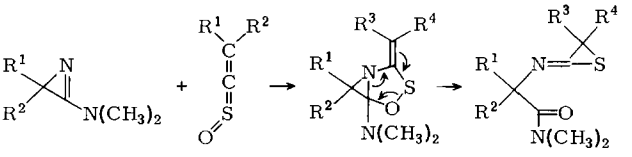
A Novel Method for the Synthesis of Thiiranimines**

By *Ernst Schaumann**, *Hildegard Nimmesgern*, and *Gunadi Adiwidjaja*

Thiiranimines—heterocyclic analogs of methylenecyclopropanes—have hitherto been the subject of very few investigations[1]. We have now found that reaction of 3-dimethylamino-2*H*-azirines **1** with thioketene *S*-oxides **2** provides a surprisingly simple entry to the thiiranimine system **4**. Probably a 1,3-dipolar cycloaddition first takes place with formation of the (not isolated) highly strained bicycle **3**, which then rearranges to **4**. The yields of **4** are generally very good (Table 1); side reactions occur only in the case of 2-methyl-2-phenylazirine **1c**. That the 2-monosubstituted azirine **1b** also reacts smoothly is remarkable, for reactions of this compound normally include hydrogen shifts[4].



1 **2** **3** **4**

Scheme 1. **1a**, $R^1 = R^2 = CH_3$; **1b**, $R^1 = CON(CH_3)_2$, $R^2 = H$; **1c**, $R^1 = CH_3$, $R^2 = C_6H_5$; **2a**, $R^1 = CH(CH_3)_2$, $R^2 = C(CH_3)_3$; **2b**, $R^1 + R^2 = -C(CH_3)_2-(CH_2)_3-C(CH_3)_2-$; **2c**, $R^1 = R^2 = C(CH_3)_3$.

Table 1. Thiiranimines **4** from **1** and **2** (see Scheme 1).

4	R^1	R^2	R^3	R^4	Yield [%]	M.p. [°C]	IR $\tilde{\nu}$(C=N)
a	CH_3	CH_3	$CH(CH_3)_2$	$C(CH_3)_3$	96	34	1730
b	CH_3	CH_3	$-C(CH_3)_2-(CH_2)_3-C(CH_3)_2-$		93	69	1735
c	CH_3	CH_3	$C(CH_3)_3$	$C(CH_3)_3$	91	72	1715
d	$CON(CH_3)_2$	H	$-C(CH_3)_2-(CH_2)_3-C(CH_3)_2-$		80	97	1745, 1725
e	$CON(CH_3)_2$	H	$C(CH_3)_3$	$C(CH_3)_3$	71	oil	1730
f	CH_3	C_6H_5	$-C(CH_3)_2-(CH_2)_3-C(CH_3)_2-$		11	136	1730

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As is to be expected for the case of an exocyclic double bond on the three-membered ring[5], the C=N stretching vibration of the products **4** appears at relatively high wave-number (Table 1). An X-ray structure analysis has been carried out on **4f** (Fig. 1). Most striking, though also observed with other hetero-analogous methylenethiiranes[1], are the S—C2 bond length, which markedly exceeds the sum of the covalent radii, and the particularly small bond angle at the sulfur. The exocyclic C=N bond is somewhat shorter than in cyclic thioimidic esters[7].

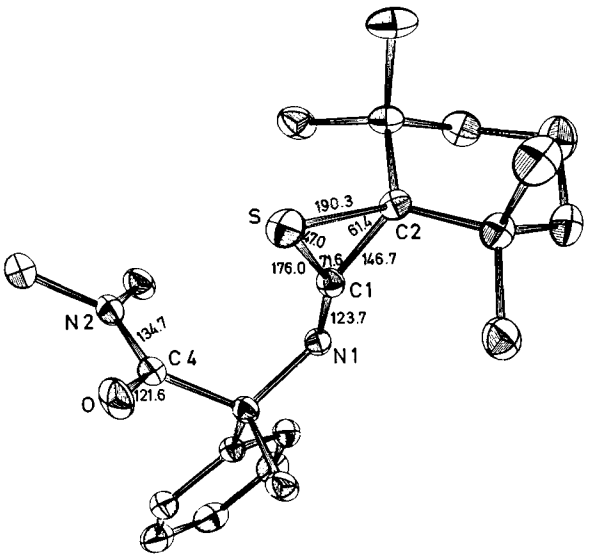

Fig. 1. Molecular structure of **4f** in the crystal, with most important bond lengths [pm] and angles [°] (ORTEP diagram).

The thiiranimines **4** are thermally relatively stable. **4a** cannot be desulfurized, even by heating (diethyl ether, 35 °C, 48 h) with tributylphosphane.

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Simple Transformation of the Azulene System into the Pentalene System**

By *Klaus Hafner** and *Michael Goltz*

Dedicated to Professor Hermann Stetter on the occasion of his 65th birthday

Cycloaddition reactions of the azulene system **1** with electron-poor and electron-rich alkynes provide a simple entry to derivatives of heptalene **2**[1] and cyclopentacyclononene **3**[2]. We have recently also been able to accomplish the transformation of **1** into the pentalene system **4**.

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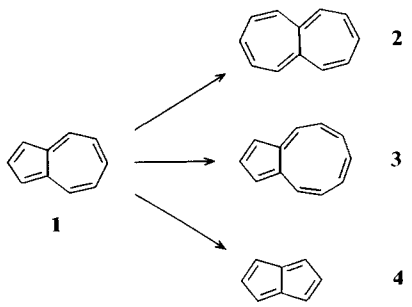
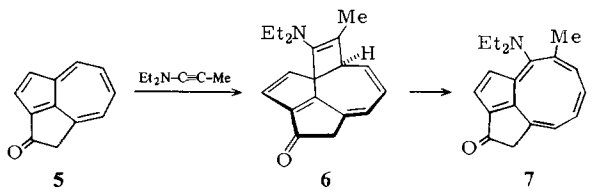
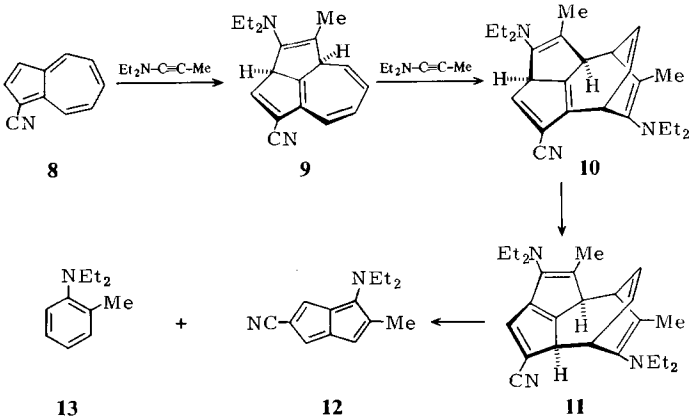
In the homologization of azulene with 1-diethylaminopropyne (**1**→**3**) electron-acceptors in the 1-position strongly influence both the rate as well as the course of the cycloaddition. 2-Oxo-1,2-dihydrocyclopenta[*cd*]azulene



5[3] reacts with 1-diethylaminopropyne even at 25 °C in dichloromethane (14 h) or in benzene (4 d), presumably in a dipolar [2+2]-cycloaddition, to give the non-isolable adduct **6**; valence isomerization of **6** then affords 5-*N*,*N*-diethylamino-6-methyl-2-oxo-1,2-dihydrocyclonona[*cd*]-pentalene **7** (golden yellow crystals, m.p. 167—169 °C (dec)) in 60 or 80% yield, respectively[4,5a]. The analogous reaction of the 1,2-dihydrocyclopenta[*cd*]azulene yields only 43% of the corresponding ring-expansion product after about 20 d[2].



In contrast, 1-azulenecarbonitrile **8** reacts with the same ynamine at 25 °C in dichloromethane (15 min) to give the 4-(*N*,*N*-diethylamino)-5-methyl-2-pentalenecarbonitrile **12** (30%, olive-green crystals, m.p. >110 °C (dec))[5b], which is stable at room temperature and on exposure to air, together with 38% *N*,*N*-diethyl-*o*-toluidine **13**[5c]. In contrast to **5**, the azulene **8** apparently adds the ynamine in the 3,4-position to give the dihydrocyclopenta[*cd*]azulene derivative **9**, whereby the cycloaddition, as in the formation of **6**, may be initiated by a nucleophilic attack of the electron-rich alkyne in the 4-position of the azulene system. This presumably reacts in a subsequent Diels-Alder reaction with inverse electron-demand to give the 1:2 adduct **10**. Isomerization to **11** followed by cycloreversion finally



yields the pentalene **12**, stabilized by donor and acceptor groups, as well as **13**.

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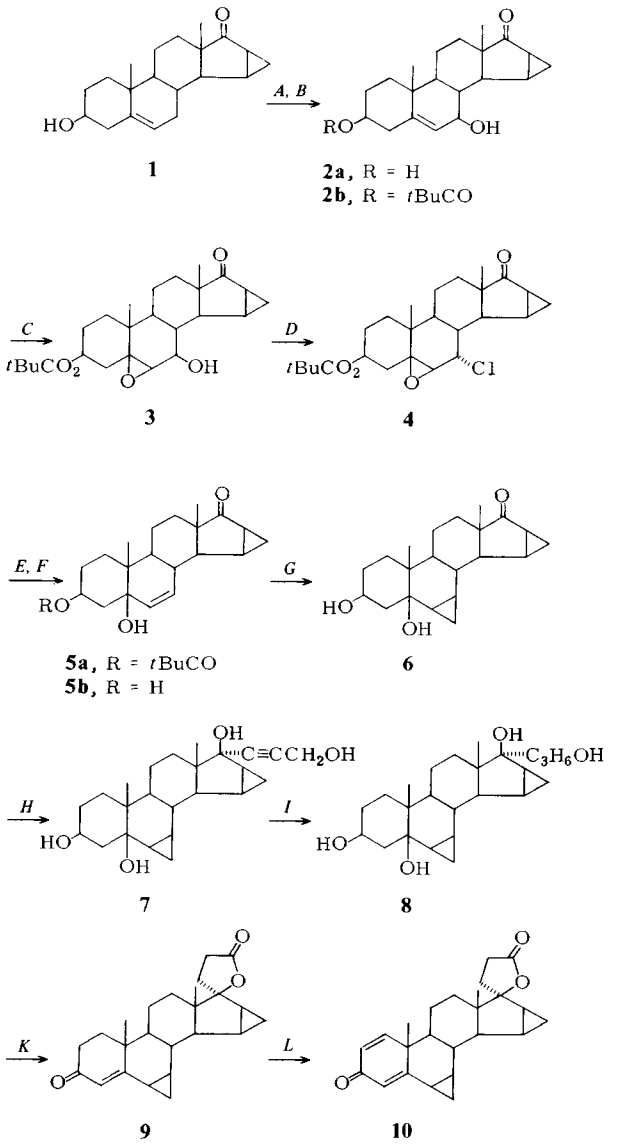
[3] K. Hafner, K.-P. Meinhardt, W. Richarz, *Angew. Chem. 86* (1974) 235; *Angew. Chem. Int. Ed. Engl. 13* (1974) 204.
[4] All the compounds isolated gave correct elemental analyses. The structure of 7 was confirmed by an X-ray structure analysis.
[5] a) 100 MHz-^{1}H-NMR spectrum ($CDCl_3$): $\delta = 1.4$ (2t, superimposed, $J = 7$ Hz, 6H, CH_2—CH_3); 1.71 (s, 3H, CH_3); 3.12 (d, $J = 20$ Hz, 1H, CO—HCH); 3.7 (m, 3H, CO—HC*H* + CH_2—CH_3); 4.16 (q, $J = 7$ Hz, 2H, CH_2—CH_3); 5.5, 5.95 (2m, 4H, H-6, H-7, H-8, H-9); 6.50 (s, 2H, H-2,3). 25.2 MHz-^{13}C-NMR spectrum ($CDCl_3$): $\delta = 12.2$ (CH_2—CH_3); 12.7 (CH_2—CH_3); 22.3 (CH_3); 44.7 (CH_2—CH_3); 45.3 (CH_2—CH_3); 50.4 (CO—CH_2); 109.0 (C—H); 109.3 (quart. C); 113.4 (C—H); 122.5 (C—H); 124.0 (C—H); 127.4 (C—H); 132.2 (C—H); 134.0 (quart. C); 136.7 (quart. C); 139.2 (quart. C); 151.3 (quart. C); 172.9 (quart. C); 194.2 (quart. C). UV/VIS spectrum (dioxane): λ_{max} ($\lg\varepsilon$) = 240 (4.06); 258 (4.09); 290 (sh, 4.09); 315 (4.15); 385 (4.23) nm.—b) 60 MHz-^{1}H-NMR spectrum ($CDCl_3$): $\delta = 1.35$ (t, $J = 7$ Hz, 6H, CH_2—CH_3); 1.93 (d, $J = 1.5$ Hz, 3H, CH_3); 3.3–3.9 (2q, superimposed, $J = 7$ Hz, 4H, CH_2—CH_3); 5.70 (s, 1H); 6.1 (m, 1H); 6.27 (s, 1H). 25.2-MHz ^{13}C-NMR spectrum ($CDCl_3$): $\delta = 10.4$ (CH_2—CH_3); 14.9 (CH_2—CH_3); 17.4 (CH_3); 46.8 (CH_2—CH_3); 50.1 (CH_2—CH_3); 98.1 (quart. C); 116.5 (quart. C); 118.9 (C—H); 120.7 (quart. C); 130.2 (C—H); 131.2 (quart. C); 136.2 (quart. C); 142.1 (C—H); 165.2 (quart. C, C—$N(C_2H_5)_2$). UV/VIS spectrum (dioxane): λ_{max} ($\lg\varepsilon$) = 273 (4.53); 398 (sh, 4.04); 411 (4.16); 431 (4.09); 630 (2.62) nm.—c) See M. Goltz, Diplomarbeit, Technische Hochschule Darmstadt 1981.



Scheme 1. *A: Botryodiplodia malorum*, substrate concentration 1 g/L, fermentation time 40 h; *B:* $[(CH_3)_3CCO]_2O$, dimethylaminopyridine in pyridine, RT, 72 h; *C: tert*-butyl hydroperoxide, $VO(C_5H_7O_2)_2$ in toluene, 80 °C, 2 h; *D:* $P(C_6H_5)_3$ in CCl_4/CH_2Cl_2/pyridine, 0 °C→RT, 2 h; *E:* Zn powder in Ac_2O/tetrahydrofuran (THF), 70 °C, 1.5 h; *F:* KOH, $NaClO_4$ in THF/MeOH, RT, 2.5 h; *G:* ZnCu, CH_2I_2 in ethylene glycol dimethyl ether, 55 °C, 5 h; *H:* HC≡CCH_2OH, KOEt in THF, RT, 2 h; *I:* $Pd/CaCO_3$, H_2 in THF/2-propanol, RT, 1 bar, 2 h; *K:* pyridinium dichromate in DMF, 70 °C, 24 h; L: DDQ in dioxane, 100 °C, 1.5 h.—Yields [%], melting points [°C] (Mettler FP11, 2 °C/min), and $[\alpha]_D^{22}$ values [°] ($c = 0.5$ in $CHCl_3$): **2a**: 55, 229.5, −51; **2b**: 65, 336.0, −45; **3**: 98, 220.0, −12; **4**: 79, 228.3, −100; **5a**: 75, 247.5, −24; **5b**: 94, 202.4, −78; **6**: 88, 210.9, −34 ($c = 0.5$ in EtOH); 7: 69, 198.5 −87 ($c = 0.5$ in EtOH); **8**: 95, 181.3, −25; **9**: 62, 201.3, −182; **10**: 59, 259.8, −159.

Synthesis of Spirorenone—A Novel Highly Active Aldosterone Antagonist

By *Dieter Bittler, Helmut Hofmeister, Henry Laurent, Klaus Nickisch, Robert Nickolson, Karl Petzoldt,* and *Rudolf Wiechert**

Spironolactone (7α-acetylthio-3-oxo-17α-pregn-4-ene-21,17-carbolactone)[1] is a competitive antagonist of aldosterone, the most active natural mineralocorticoid. It has been used therapeutically for approximately twenty years to treat edamatous diseases and essential hypertonia. As a side effect—particularly when used over longer periods of time and at higher doses—endocrinological disorders have been observed, which can be attributed to antiandrogenic and to progestational properties of the compound. In the search for an aldosterone antagonist having increased main activity without relevant side effects, we synthesized 6β,7β:15β,16β-dimethylene-3-oxo-17α-pregna-1,4-diene-21,17-carbolactone, **10**, spirorenone.

The starting material **1**[2], which was hydroxylated microbiologically in the 7β-position using the fungal strain *Botryodiplodia malorum*, was obtained from 3β-hydroxy-5,15-androstadien-17-one by Corey cyclopropanation. Selective esterification of the 3β-hydroxy group of **2a** was performed using pivalic anhydride. According to *Hanson et al.*[3], 7β-hydroxy-Δ^5-steroids react stereospecifically with *tert*-butyl hydroperoxide under vanadium(IV) oxide-acetylacetonate catalysis to afford 5β,6β-epoxides, which can be converted by treatment with Ph_3P/CCl_4 in pyridine into 7β-chloro derivatives. Applying this reaction sequence to **2b** gave the chloro epoxide **4**, which yielded the 5β-hydroxy-Δ^6-derivative **5a** upon reductive elimination of the chlorine atom (Zn/CH_3CO_2H). Saponification with KOH/$NaClO_4$ in methanol results in formation of the 3β,5β-diol **5b**, the key compound for stereospecific cyclopropanation using the Simmons-Smith method (**5b**→**6**)[4]. To form the spirolactone ring, propargyl alcohol was added to the ketone **6**. Hydrogenation of the triple bond followed by oxidation of the tetrol **8** with pyridinium dichromate in dimethylformamide (DMF) led, *via* formation of the α,β-unsaturated ketone and the lactone ring, to compound **9** [UV

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(MeOH): $\varepsilon_{265} = 19000$; characteristic ^{1}H-NMR data ($CDCl_3$): $\delta = 0.40-0.67$ (m, 1H, cyclopropyl H), 1.01 (s, 3H, 18-H), 1.11 (s, 3H, 19-H), 6.04 (s, 1H, 4-H)]. The lactone **9** was dehydrogenated using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford **10** [UV (MeOH): $\varepsilon_{245} = 12100$, $\varepsilon_{286} = 9950$; characteristic ^{1}H-NMR data ($CDCl_3$): $\delta = 0.42-0.69$ (m, 1H, cyclopropyl H), 1.04 (s, 3H, 18-H), 1.15 (s, 3H, 19-H), 6.18 (dd, $J = 10$ and 2 Hz, 1H, 2-H), 6.34 (d, $J = 2$ Hz, 1H, 4-H), 6.88 (d, $J = 10$ Hz, 1H, 1-H].

The spirolactone derivatives **9** and **10** exhibit in humans an activity equal to *ca.* 5 times that of spironolactone, which corresponds to the activity of these substances found in the rat. Whereas tests with animals indicate that **9** exhibits both progestational and antiandrogenic effects, comparable doses of spirorenone **10** exhibit no antiandrogenic and considerably weaker progestational activity[5].

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$[Ag_5I_6]^-$, A One-Dimensional Infinite Anion with 10_5 mc Symmetry

By *Karl Peters, Walter Ott,* and *Hans Georg von Schnering**

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

We have been able to detect polymeric anions $[Ag_nI_{n+1}]^-$ formed during the synthesis of complex silver iodides with large organic cations in organic bases. Structural studies revealed that in these anions AgI_4 tetrahedra are condensed to give one-dimensional infinite polyanions[1,2]. These compounds contain, in part, the anion $^1_\infty[Ag_2I_3]^-$, which was previously obtained as the cesium salt in aqueous solution[3,4].

In the light of the previous reports, the existence of the novel polyanion $^1_\infty[Ag_5I_6]^-$ is surprising. This anion, which has been detected in two compounds for the first time, has a fascinating topology (Fig. 1). $^1_\infty[Ag_5I_6]^-$ has a 10_5 mc rod group symmetry, formed by the cyclocondensation of two groups of 5 AgI_4 tetrahedra. Every group of 5 AgI_4 tetrahedra has an iodine atom in common which occupies the center of the decagonal channel. This atom can be viewed as the additional $I^- : {}^1_\infty[(AgI_{3/3}I_{1/5})_5]^-$. The intensity distribution of the X-ray reflections in the projections parallel to the one-dimensional channel exhibits the Fourier transform of a tenfold structural unit.

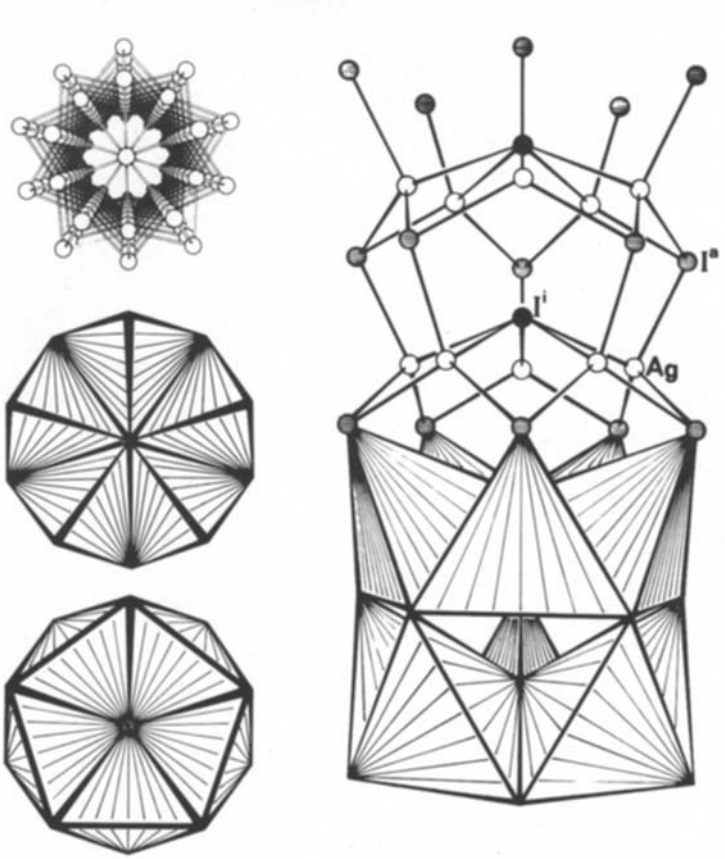

Fig. 1. The polymeric anion $^1_\infty[Ag_5I_6]^-$. Left (top): view along the 10_5 screw axis, sequence of atoms from inside to outside is I^i-Ag-I^a; (middle, bottom): under- and topside of the five condensed AgI_4 tetrahedra. Right: view perpendicular to the decagonal channel.

Both compounds with $[Ag_5I_6]^-$ are formed from a suspension of AgI in the basic solvents L (L = *N,N*-diethylacetamide or *N*-methyl-2-pyrrolidinone) following addition of hydriodic acid, and precipitate as colorless needles upon subsequent addition of acetone. The crystals contain $HAg_5I_6 \cdot 2L$; X-ray structural analysis does not permit determination of the location of the proton. The decagonal columns of anions are arranged parallel to the needle axis and in both crystals form the framework of a primitive-square rod packing, in whose gaps the (in part, protonated) organic bases are located.

In both compounds the Ag—I bond lengths in the polymeric anion differ only slightly and are 297.3 pm, on average, to the central I atom, and 284.2 pm, on average, to the peripheral I atoms.

The structure of this channel-like polymeric anion is a good example for the formation of a symmetry, which is disallowed in 3 D space groups, by reduction of the dimensionality. The assignment of the I^- to the center of the channel is reminiscent of the linear chains of iodine in other compounds[5,6]. They offer an opportunity for modifications—for example by redox reactions.

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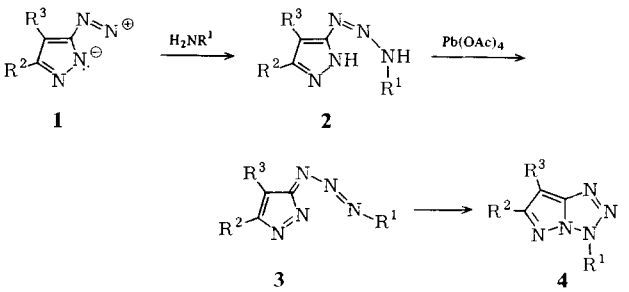
A Ring Building-Up Synthesis of *N*-Glycosides: Dehydrogenation of Glycosyltriazeno-1*H*-pyrazoles**

By *Günter Ege**, *Karlheinz Gilbert*, and *Reinhard Heck*

Dedicated to Professor Hermann Schildknecht on the occasion of his 60th birthday

In the ring building-up synthesis of *N*-glycosides[2c] the heterocycle is synthesized after the glycosidation step. We report here on a synthetic route which leads to 3*H*-pyrazolo[1,5-*d*]tetrazoles **4**, and which makes *N*-glycosides of this heterobicyclic system as well as related substitution products accessible. 3-Diazo-3*H*-pyrazoles **1** react with primary amines to give 3-mono-substituted 1-pyrazolyltriazenes **2**, which in some cases crystallize out from the reaction solution (CH_2Cl_2) (*e.g.* with $R^2=CH_3$, $R^3=C_6H_5$ when $R^1=4$-$O_2NC_6H_4$ and $R^1=CH_2CO_2CH_3$). Dehydrogenation of the triazenes **2**[3] in solution or in suspension with lead(IV) acetate furnishes the colorless to orange-yellow pyrazolotetrazoles **4**.

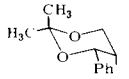
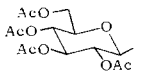
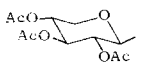
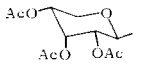


1 **2** **3** **4**

This new method for the synthesis of the bicyclic ring system **4** is especially attractive owing to the wide variability that is possible with respect to R^1, R^2, and R^3 (Table 1). Reactions of tetra-*O*-acetyl-2-deoxy-2-glucosamine and of *O*-acetylated pento- and hexo-1-pyranosylamines afford the glycosides **4j—4n**. In the case of **4k—4n** the ^{1}H-NMR spectra ($J_{1,2}=8.5$—9.5 Hz) reveal that the heterocycles are β-glycosidically linked with the sugar moieties. The *N*-glycosides **4k—4n** are stable in the crystalline state, but in protic solvents ring-opening with splitting off of the sugar moiety slowly takes place, giving the corresponding 3-azido-1*H*-pyrazole.

In the course of the novel ring synthesis **1**→**4** the nitrogen atom of a primary amine is incorporated into the heterobicycle in a [7+1]-cycloreaction[5]; a coupling reaction (**1**→**2**) and dehydrogenation (**2**→**3**) are followed by a 1,8-electrocyclization[7] to the 1,2,3,3a,4-pentaazapentalene system **4**.

Table 1. Yields and melting points of **4a—4n**; $R^2=CH_3$ [a].

4	R^1	R^3	Yield [%]	M.p. [°C]
a	4-$O_2NC_6H_4$—	C_6H_5	69	215-217
b	3-$F_3CC_6H_4$—	C_6H_5	78	150-152
c	$CH_3O_2CCH_2$—	C_6H_5	61	139-140
d	$CH_3O_2CCH_2$—	CH_3O_2C	54	121-123
e	$HOCH_2CH_2$—	C_6H_5	65	126-128
f		C_6H_5	63	154-156
g		C_6H_5	58	103-104
h		CH_3O_2C	81	98-100
i [b]		Br	60	151-153
j		C_6H_5	45	146-147
k		C_6H_5	58	122-123
l [b]		Br	61	133-136
m		C_6H_5	37	141-143
n		C_6H_5	21	122-124

[a] All compounds gave correct elemental analyses and spectroscopic data. The yields are referred to 1*H*-pyrazol-3-amines, precursors of **1**. [b] $R^2=H$.

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Alkyl-Substituted 3,4-Dihydro-2*H*-pyrans: Mass Spectroscopy, Synthesis, and Identification as Insect Constituents**

By *Wittko Francke** and *Wolfgang Mackenroth*

Dedicated to Professor Hermann Schildknecht on the occasion of his 60th birthday

Many of the known insect constituents with nitrogen heterocycles having five- and six-membered ring structures are apparently formed from oxygen-containing precursors. Hence, cyclic azomethines[1,2] may be formed from hydroxy ketones. Direct cyclization of these precursors should lead to cyclic enol ethers not previously isolated from insects. In order to facilitate the identification of sub-

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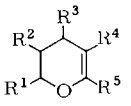
stances of this type in biological material we studied the mass spectroscopic fragmentation of alkyl-substituted 3,4-dihydro-2*H*-pyrans **1**.



	R^1	R^2	R^3	R^4	R^5
1a	Me	H	H	H	Me
1r	Et	Me	H	Me	Et

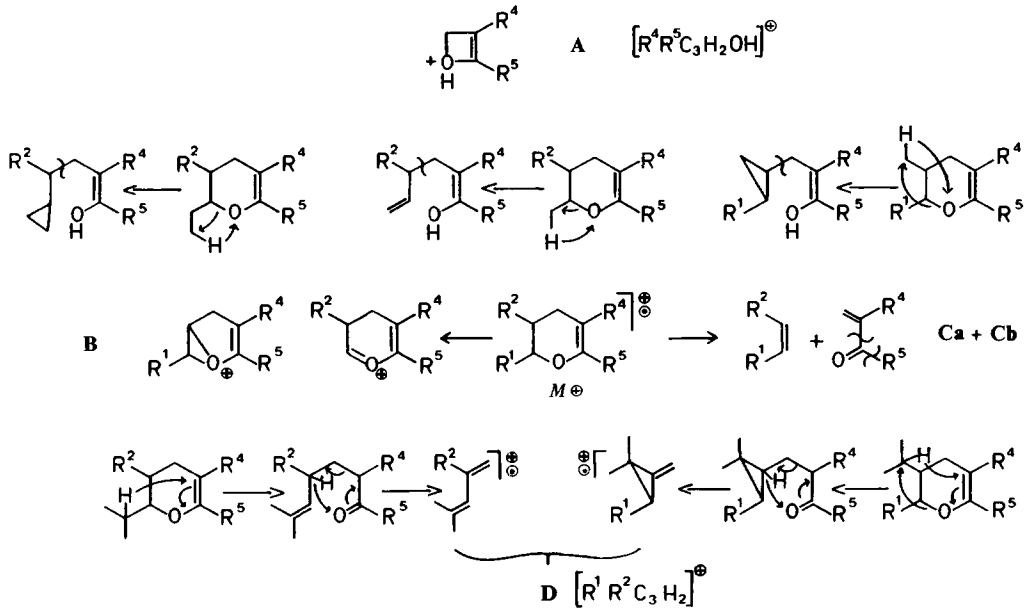
Scheme 1 shows the key ions of these compounds. Additional fragments are less significant. The exact composition of all the ions was determined by high resolution techniques. All of the hydrogen shifts exhibited in Scheme 1 were corroborated by deuterium labeling. Although the structures of the ions are unknown, proposals were made, which reflect elements of the starting structures, in order to give a clear indication of the original substitution pattern.

fragments, occur relatively frequently; occasionally, intense daughter ions from **C** occur.

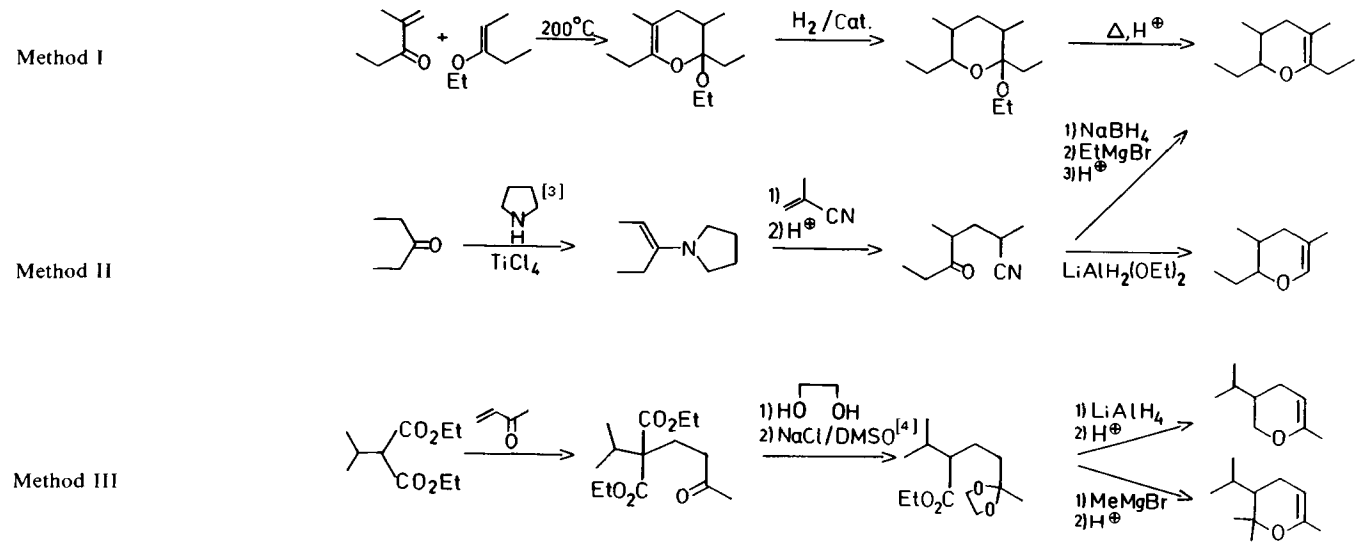
The ions **A** and **D** are formed after hydrogen shift, particularly from substituents R^1 and R^2; their intensity is therefore strongly dependent upon the substitution pattern. If R^1 is ethyl or a higher alkyl moiety, **A** often becomes the base peak of the spectrum.

The alkyl substituted 3,4-dihydro-2*H*-pyrans **1** were synthesized as outlined in Scheme 2.

We were also able for the first time to identify the 3,4-dihydro-2*H*-pyrans **1a** and **1r** as insect constituents. The extremely volatile **1a** occurs in the heads of female honeybee workers *Apis mellifica*, whereas **1r** is a sex pheromone of the female cigarette beetle *Lasioderma serricorne*. In behavioral studies[8], racemic **1r** exhibited a 10^3fold biological activity relative to the open-chain hydroxy ketone[9], which also occurs in the cigarette beetle.



Scheme 1. Schematic representation of the fragmentation pattern of the alkyl-substituted 3,4-dihydro-2*H*-pyrans **1**.



Scheme 2.

All the spectra display pronounced molecular ion peaks and, as expected, intense ions **B**. The products **C** of the retro Diels-Alder cleavage, in particular the hydrocarbon

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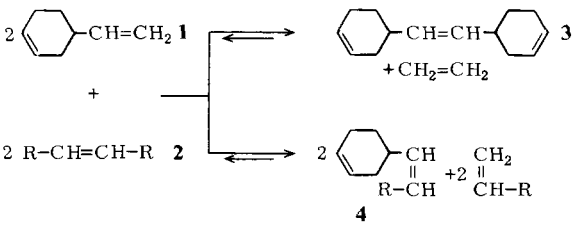
Synthesis of Primary Alkylarenes without Benzene *via* Olefin Metathesis**

By *Siegfried Warwel**, *Heinz Ridder*, and *Wolfgang Winkelmüller*

Dedicated to Professor Friedrich Asinger on the occasion of his 75th birthday

Higher alkylarenes, as important precursors of surfactants, are synthesized on an industrial scale by alkylation of benzene with higher olefins or alkyl chlorides (C_{10}—C_{13}), which always results in structural isomers being formed[3]. We have developed a new synthetic method, which does not require the use of benzene and yields exclusively primary alkylarenes (1-phenylalkanes).

The starting compound in our two-step synthesis is 4-vinylcyclohexene **1**, which is also readily accessible on an industrial scale from butadiene[5]. The carbon skeleton of the primary alkylarenes was obtained by metathesis of **1** with symmetric monoolefins **2** (catalyst: $WCl_6/Et_2O/Sn(n\text{-}C_4H_9)_4$ or Re_2O_7/Al_2O_3).



Of the two possible parallel reactions—homometathesis of **1** to give 1,2-dicyclohexenylethylene **3** and co-metathesis of **1** with **2** to give 1-(3-cyclohexenyl)-1-alkenes **4**—the latter with excess **2** proved to be markedly preferred (see Table 1).

Table 1. Metathesis of 4-vinylcyclohexene **1** with symmetric olefins **2** to give **4** [a].

R	**2**	Conversion of **1** [%]	Selectivity **1**→**4** [%]
CH_3	2-Butene	84	92
$n\text{-}C_4H_9$	5-Decene	84	84
$n\text{-}C_6H_{13}$	7-Tetradecene	82	91
$n\text{-}C_8H_{17}$	9-Octadecene	80	86

[a] Catalyst: $WCl_6 : Et_2O : Sn(n\text{-}C_4H_9)_4 = 1:1:2$; $WCl_6 : \mathbf{1} : \mathbf{2} = 1:165:330$; $CHCl_3$ as solvent: 50 °C; 1 h.

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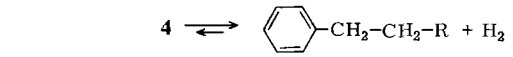
[**] Olefin Metathesis, Part 9. This work was supported by the Minister für Wissenschaft und Forschung des Landes Nordrhein Westfalen and the Fonds der Chemischen Industrie. Part 8: S. Warwel, E. Janssen, *Chem.-Ztg. 106* (1982) 266.

With exception of 2-butene, the symmetric olefins **2** employed were prepared by metathesis of α-olefins according to [7]:

$$2\,R\text{—}CH{=}CH_2 \rightleftharpoons \mathbf{2} + CH_2{=}CH_2$$

For the synthesis **4**, however, the α-olefins also could be used directly.

The conversion of **4** into primary alkylarenes was achieved by isomerizing dehydrogenation on K/Al_2O_3 ($K:\mathbf{4} = 1:10$; 120 °C; 2 h; conversion: 100%; selectivity 88—95%).



The isomerization catalyst Na/Al_2O_3 employed by *Ruckelshauss* and *Kosswig*[10] for the synthesis of ethylbenzene from **1** was not active enough. A substantial improvement of this synthetic step was possible with typical hydrogenation-dehydrogenation catalysts. Independent of the chain length of the alkenyl group, **4** could be converted in the gas phase at 350 °C on Pd/Al_2O_3 or Pt/Al_2O_3 in a continuous flow reactor into primary alkylarenes with conversions of >99% and selectivities of 95–98%.

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Heterocyclic Radical Anions as Ligands: An Unexpected Change of Coordination in Pentacarbonylmetal Complexes

By *Wolfgang Kaim** and *Volker Kasack*

Heterocyclic π radical anions may act as substituents in carbonylmetal complexes: The σ-coordination *via* the lone pairs of the heteroatom is complemented by the π backbonding from the metal to the half-filled ligand molecular orbital. In the course of studies[1] using hexacarbonylchromium, -molybdenum, and -tungsten we have reacted these complexes in tetrahydrofuran (THF) with reduced 2,1,3-benzochalcogenadiazoles **1**[2]. Formally, these ligands consist of a radical-stabilizing organic part and of an inorganic coordinating component.

The ESR spectroscopic investigation of the substitution behavior has now revealed a remarkable change in the coordination mode. *N,N'*-dicoordinated 1:2 complexes **3** were observed for eight of the nine possible combinations, in some cases the 1:1 intermediate complexes **2** could be identified, too. Spectroscopic effects expected for the $(OC)_5M$ coordination[1] have been observed, such as the occurrence of metal isotope coupling, the increase of the ^{14}N splitting, or the characteristic dependence of g on the nature of the metal (Table 1).

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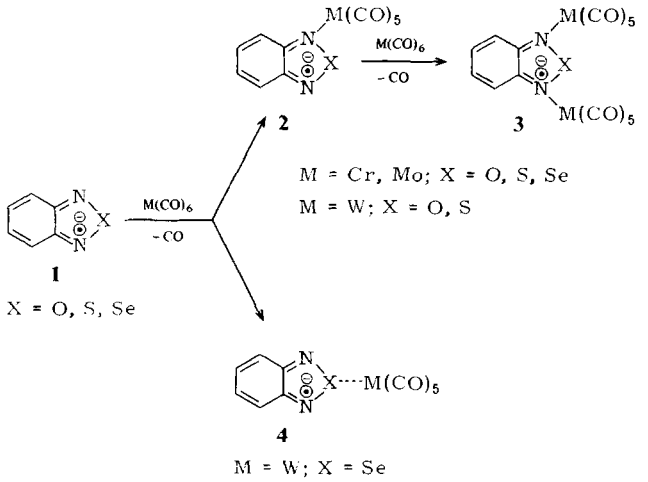

Table 1. ESR data of radical complexes **1**, **3**, and **4**; coupling constants a_x in mT.

Radical	X	M	$a_{H(4)}$	$a_{H(5)}$	a_N	a_M [a]	g
1 [2]	O	—	0.351	0.218	0.561	—	[b]
3	O	Cr	0.243	0.206	0.710	0.056	2.0042
3	O	Mo	0.245	0.206	0.713	0.124	2.0045
3	O	W	0.215	0.202	0.703	0.200	2.0062
1 [2]	S	—	0.259	0.159	0.518	—	[b]
3	S	Cr	0.186	0.160	0.650	0.040	2.0043
3	S	Mo	0.176	0.155	0.633	0.087	2.0046
3	S	W	0.16	0.16	0.640	0.150	2.0065
1 [2]	Se	—	0.248	0.165	0.579	—	[b]
3	Se	Cr	0.17	0.17	0.720	[b]	2.0042
3	Se	Mo	0.16	0.16	0.700	0.098	2.0045
⇒ **4**	Se	W	0.225	0.112	0.641	[b]	2.0056

[a] ^{53}Cr: 9.5%, $I = 3/2$; ^{95,97}Mo: 25.4%, $I = 5/2$; ^{183}W: 14.3%, $I = 1/2$. [b] Not observed or reported.

In contrast, the paramagnetic complex **4** formed on reaction of $W(CO)_6$ with **1**, X = Se, displays a rather different spectroscopic behavior: The ESR splitting pattern (Fig. 1) indicates an at least C_s- or C_2-symmetric species, and the large line width suggests the presence of Se[3]; however, the ^{14}N splitting is significantly smaller than that expected for an *N*-coordination (Tab. 1). The relatively small g value suggests coordination of only *one* $(OC)_5W$ fragment, and finally, the ^{1}H coupling constants are very different from each other (cf. however complexes **3**).

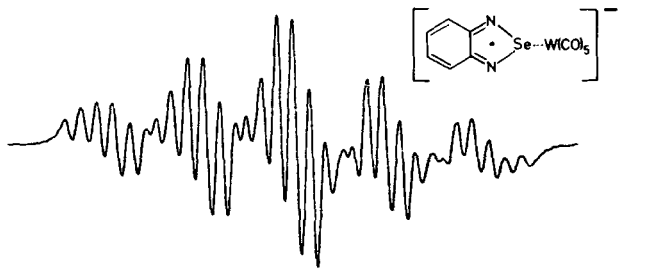

Fig. 1. ESR spectrum of the radical complex **4** at 300 K in THF, counter ion K^+.

The similarity of spin distributions in **4** and in the ligand radical **1**, X = Se, indicates also that the spin bearing π system does not essentially participate in the metal carbonyl coordination. Considering these arguments, we infer a σ coordination of $(OC)_5W$ at the selenium atom[4]; it is especially noteworthy that this differing coordination occurs only with the combination of the heaviest atoms.

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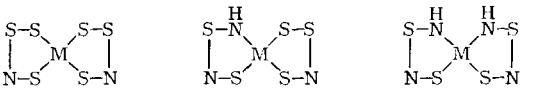
$[(S_3NNi)_3S_2]^{\ominus}$—A Ni_3S_2 Cluster with $S_3N^{\ominus}$ Chelate Ligands**

By *Johannes Weiss**

Dedicated to Professor Hermann Schildknecht on the occasion of his 60th birthday

Mononuclear complexes such as **1** and **2** with the chelate ligand $[S=N—S—S]^{\ominus}$ have been known for some time as by-products in the synthesis of the M^{II} complexes **3**[1].



Compounds with $S_3N^{\ominus}$ are accessible, however, in other ways[2]. Thus, *Bojes* and *Chivers*[2b] prepared $S_3N^{\ominus}$ from $S_4N^{\ominus}$, which in turn can be obtained from S_7NH[3].

We have now found that metal complexes with the chelate ligand $S_3N^{\ominus}$ can be prepared in alkaline media, without isolation of intermediates, starting from S_7NH. Surprisingly, a trinuclear complex $[(S_3NNi)_3S_2]^{\ominus}$, in which the three $>NiS_3N$ moieties are bridged by two sulfur atoms, is formed in this way with $NiCl_2$. This anion can be isolated as a stable, readily crystallizing tetra-*n*-butylammonium salt[4], whose structure was obtained by X-ray crystallography[5].

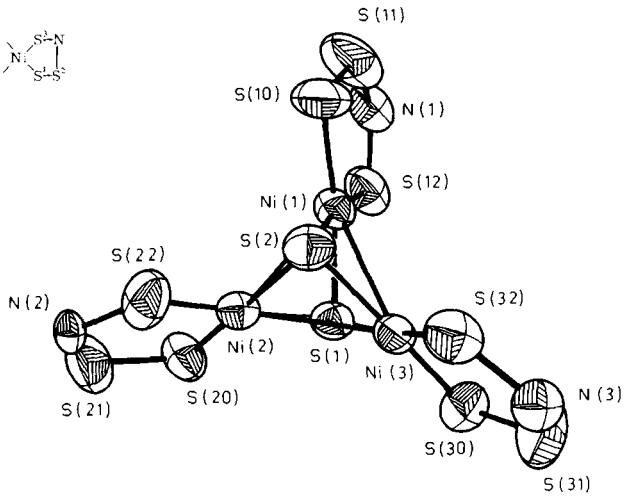


Fig. 1. Structure of the complex anion $[(S_3NNi)_3S_2]^{\ominus}$ in the tetrabutylammonium salt. Average distances [pm]: Ni—Ni 290.4(44), Ni—μ_3-S 220.1(3), Ni—S^1 212.3(2), S^1—S^2 201.4(15), Ni—S^3 212.0(3), S^2—N 145.2(47), S^3—N 175.3(13).

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[**] Metal Sulfur-Nitrogen Compounds, Part 12.—Part 11: K. Hornemann, J. Weiss, *Angew. Chem. 94* (1982) 645; *Angew. Chem. Int. Ed. Engl. 21* (1982) 633.

The complex anion does not possess three-fold symmetry, but only approximate C_s symmetry with S(1), S(2), S(10), S(11), S(12), and N(1) in the mirror plane. The almost planar chelate ligands are located at right angles to the plane through the three Ni atoms; two of the three N atoms lie above, and the third (N(1)) below this plane.

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[4] Procedure: A solution of S_7NH (1 g, 4.2 mmol), $NiCl_2 \cdot 6H_2O$ (0.75 g, 3.2 mmol) and KOH (0.4 g, 7.2 mmol) in 100 mL of methanol is stirred for 2 h. The brown-red solution is filtered off and evaporated to dryness, and the residue extracted with 100 mL of hot benzene to remove excess S_7NH and by-products: the main product is dissolved in 2 × 10 mL of acetone, filtered, and evaporated to dryness. The residue is dissolved in a small amount of methanol and precipitated as the tetrabutylammonium salt by addition of a saturated solution of $[nBu_4N]Br$. Purification was carried out by recrystallizing from methanol: thin, black platelets (m.p. = 149 °C), which appear reddish in transmitted light, are formed.

[5] Monoclinic, $P2_1/c$, $a = 978.3(3)$, $b = 1847.3(5)$, $c = 1919.3(2)$ pm, $\beta = 103.69(2)°$, $Z = 4$. Measurements made using a Syntex R3 diffractometer, 2803 independent reflections with $I > 2.5\sigma(I)$; R_w (anisotropic, H atoms isotropic) = 4.2%. Further details of the crystal structure determination can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen by quoting the number CSD 50225, the name of the author, and the complete citation of the journal.

A Novel Three-Dimensional Tellurium Array: High-Pressure Synthesis and Crystal Structure of $AgTe_3$**

By *Klaus-Jürgen Range**, *Manfred Zabel, Franz Rau, Freia von Krziwanek, Rupert Marx*, and *Beate Panzer*

It has long been known that the chain structure of the trigonal, semiconducting tellurium modification[1a] can be derived[1c,d] from the cubic structure of metallic α-polonium[1b] by a relatively slight atom shift. A metallic tellurium modification with α-Po structure[1c] was first discussed almost 35 years ago, but so far it has never been realized[2]. The previously unknown compound $AgTe_3$ of the Ag—Te system, which we have now synthesized under high pressures, contains a three-dimensional array of tellurium atoms that is very closely related to the α-Po structure.

We first detected $AgTe_3$ during the high-pressure decomposition of $AgGaTe_2$ in an NH_4Cl-melt (20 kbar, 900 °C, 60 min). This brittle, golden-colored substance having a metallic luster is formed in the pure state when the respective elements are allowed to react under high pressure ($P > 12$ kbar) in a modified Belt apparatus[3] at $T = 100-1200$ °C (sintered BN high-pressure capsule, 30 min) and subsequently chilled to normal conditions. $AgTe_3$ is only metastable at normal pressure; conversion into the thermodynamically stable mixture of $Ag_{5-x}Te_3$ and Te[4] proceeds quantitatively within a few minutes at 1 bar and 300 °C. This is easily recognizable—especially with larger specimens—by the abrupt transition from golden luster to silver luster.

The crystal structure of $AgTe_3$ is best interpreted in terms of an inner-centered, pseudocubic ($\alpha = 90.15°$) arrangement of the rhombohedral unit cell (Fig. 1). In this arrangement the Ag atoms occupy the center and corners, the Te atoms the face- and edge-centers of a cube. Thus the crystal structure of $AgTe_3$ is the first example of a combination of the (slightly distorted) cubic lattice complexes I and J*[5a] and it should be regarded as an ordered (1:3; Ag:Te) analogue of the α-polonium structure.

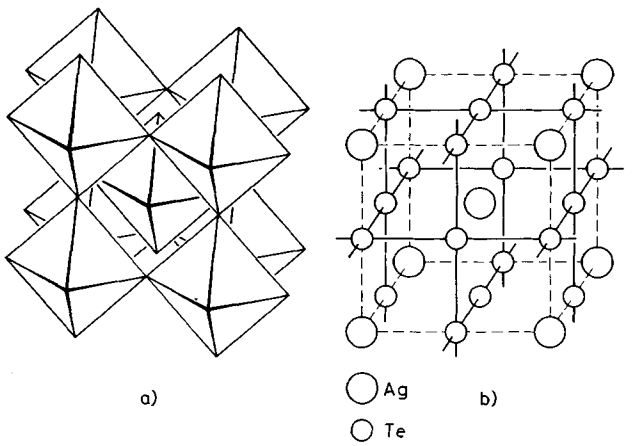

Fig. 1. Section from the crystal structure of $AgTe_3$: a) arrangement of the $AgTe_3$ octahedron, b) three-dimensional array of the tellurium atoms.—Crystallographic data ($T = 293$ K): R3m, $a = 8.645$, $c = 5.272$ Å, $\gamma = 120°$, $Z = 3$; 3 Ag in 3 *a* with $z = 0.0$, 9 Te in 9 *b* with $x = 0.1672$, $z = 0.3413$; $R = 5.53\%$ (207 reflections with $I > 2\sigma(I)$).

Ag is octahedrally coordinated by Te (Ag—Te: 3 × 302.2(5), 3 × 308.3(5) pm), each Te in turn being surrounded by a square arrangement of four further Te atoms together with two Ag atoms to give a $Te(Te_4Ag_2)$ octahedron (distances: 4 × Te—Te 305.2(5), 1 × Ag—Te 302.2(5), 1 × Ag—Te 308.3(5) pm). The Te—Te distances in the three-dimensional array of tellurium atoms are close to the value of 302 pm postulated for metallic tellurium with α-Po structure[1c]; the valence angles at Te are almost 90° (89.79, 89.84, 90.52°). The metallic luster and metallic conductivity ($\rho(20\,K) = 1.5 \times 10^{-6}$, $\rho(300\,K) = 100 \times 10^{-6}\ \Omega$ cm) show that its description as Ag-stabilized cubic tellurium is possible and has more than formal significance.

$AgTe_3$ has a phase width which strongly depends on the pressure used in its preparation. Samples prepared at 25 kbar and 1200 °C exhibit a region of homogeneity from 75.6 to 60.8 atom-% Te. At 10 kbar/1200 °C this region only extends from 75.0 to 73.0 atom-% Te. It follows from density measurements and the intensities of the X-ray reflections that no vacant Te-lattice sites occur in the phases of composition deviating from that of $AgTe_3$, but that a replacement of tellurium by silver corresponding to the formulation $Ag_{1+x}Te_{3-x}$ takes place. About one third of the tellurium in $AgTe_3$ can be replaced by selenium without the structure being changed. Attempts to prepare $CuTe_3$ and $AuTe_3$ have so far not met with success. A phase obtained as a thin film by *Luo* and *Klement*[5b] on rapidly chilling Ag—Te melts is presumably related with $AgTe_3$, but it could not be satisfactorily characterized by X-ray crystallography.

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

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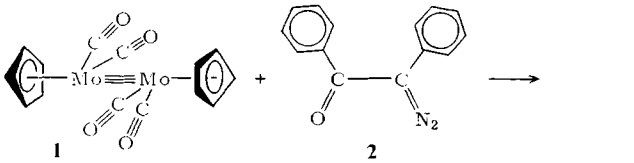
Cleavage of the Metal-Metal Triple Bond by Chelate-Forming Diazoalkane Bridges[1]

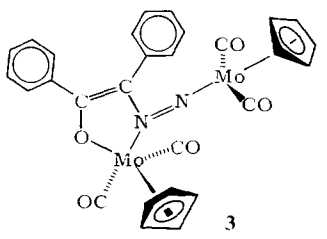
By *Wolfgang A. Herrmann**, *Gangolf W. Kriechbaum*, *Manfred Ziegler*, and *Heike Pfisterer*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

The availability of diazoalkanes to readily undergo addition of their carbene moieties to metal-metal double bonds has recently led to a convenient and high-yield standard method for the synthesis of μ-methylene complexes[2]. This type of reaction has occasionally been observed with metal-metal triple bonds too, but in this case the structure and reactivity of the resulting alkylidene complex is strongly influenced by the nature of the bridging ligands and by the peripheral ligands[3]. We now demonstrate by means of a typical example that α-diazoketones bring about cleavage of the metal-metal bond in the organometal substrate before the elimination of nitrogen and thus are suitable for the synthesis of novel *O,N*-chelate complexes having diazoalkane bridges.

Like diphenyldiazomethane[3a] and other diazoalkanes[3b,4], the α-diazoketone **2** reacts with the molybdenum complex **1** at room temperature with formation of a 1:1 adduct. From the composition and the IR and ^{1}H-NMR data the structure of a μ-diazoalkane complex containing a three-membered M_2N-ring was to be expected for





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[**] *Note added in proof* (August 12, 1982): A conventional methylene bridge is present in the complex of composition $(\eta^5\text{-}C_5Me_5)_2Mo_2(CO)_4(\mu\text{-}CH_2)(\mu\text{-}CH_2N_2)$ synthesized from **4** and CH_2N_2 (L. K. Bell, W. A. Herrmann, unpublished results 1982).

the crystalline product **3**, which can be isolated in almost quantitative yield. Surprisingly, however, the X-ray structure analysis showed that **3** fundamentally differs from all previously known organometallic diazo compounds (Fig. 1):

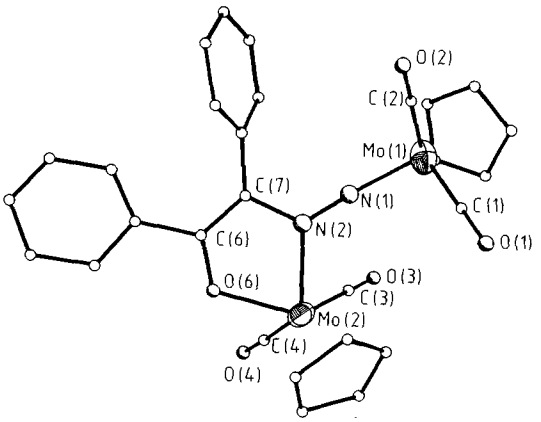


Fig. 1. Structure of the α-diazoketone complex **3** in the crystal. Selected bond lengths [pm] and angles [°]: Mo(1)—N(1) 185.8(4), Mo(2)—N(2) 218.9(4), N(1)—N(2) 125.5(6), N(2)—C(7) 143.8(6), C(6)—C(7) 137.2(7), C(6)—O(6) 131.9(6), Mo(2)—O(6) 211.5(3); Mo(1)—N(1)—N(2) 174.1(3), Mo(2)—N(2)—C(7) 116.6(3), N(2)—C(7)—C(6) 110.7(4), C(6)—O(6)—Mo(2) 118.6(3), O(6)—Mo(2)—N(2) 73.1(1), C(7)—C(6)—O(6) 120.9(4), C(1)—Mo(1)—C(2) 81.6(3), C(3)—Mo(2)—C(4) 75.1(2). — $R = 0.081$, $R_{aniso} = 0.036$.

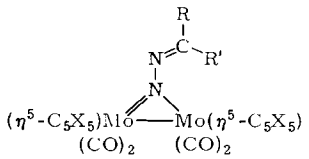
1) Coordination of the diazo ligand **2** causes irreversible cleavage of the MoMo triple bond in **1** [Mo—Mo > 380 pm]; by way of contrast, the addition of π-acidic ligands (*e.g.* diphenyldiazomethane, CO, alkynes, allene) usually proceeds with preservation of the metal-metal bond.

2) The diazo function flanking the carbonyl moiety links the two $Cp(CO)_2Mo$ fragments as a 6-electron bridging ligand which simultaneously accomplishes two very different possible modes of complexation: the terminal nitrogen atom N(1) occupies the coordination gap of the metal atom Mo(1) [Mo(1)—N(1) 185.8(4) pm], which is situated at the center of a tetrahedral coordination polyhedra. While terminal diazoalkanes are known to behave as CO-analogous ligands[12], the present mode of coordination is reminiscent of diazonium complexes of type $Cp(CO)_2M\text{—}N_2CH_3$ (M = Mo, W)[13], with the terminal nitrogen atom N(1) acting as a 3-electron donor. The same electron balance results for the chelating backbone O(6)—C(6)—C(7)—N(2) coordinated to the metal center Mo(2); however, the planar metallacycle thus formed completes a square pyramidal coordination polyhedra characteristic of compounds of type $Cp(CO)_2MLL'$. Additional coordination of the second nitrogen atom N(2) bound to the diazo-carbon might be due to a chelating effect with cooperation of the α-keto group.

Considering the results obtained with the sterically demanding methyl derivative $[(\eta^5\text{-}C_5Me_5)Mo(CO)_2]_2$ **4** as a substrate[4], the versatility of the diazoalkane reactions now manifests itself: In the initial step, the intact diazo compound coordinates *via* one or both nitrogen atoms as bridging ligand; this holds also for the reaction of **4** with **2** or diazocyclopentadiene **5**, when the complexes **6**[4] which are stable at room temperature are formed.

Depending upon the substituents R and R′, the type of structure **6** undergoes the following secondary reactions: a) N_2-elimination with formation of μ-alkylidene deriva-

tives, which as a rule are stabilized by the participation of the substituents (*e.g.* R, R′ = phenyl) in the complexation[**]; b) simultaneous CO/N_2-elimination in the case of



6, X = H, CH_3

diazoalkanes whose carbene moieties have a strong tendency to aromatize (*e.g.* diazocyclopentadiene); c) rearrangement of the diazoalkane bridges with rupture of the metal-metal bond.

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[12] Review: W. A. Herrmann, *Angew. Chem. 90* (1978) 855; *Angew. Chem. Int. Ed. Engl. 17* (1978) 800; cf. G. L. Hillhouse, B. L. Haymore, *J. Am. Chem. Soc. 104* (1982) 1537, and references cited therein.

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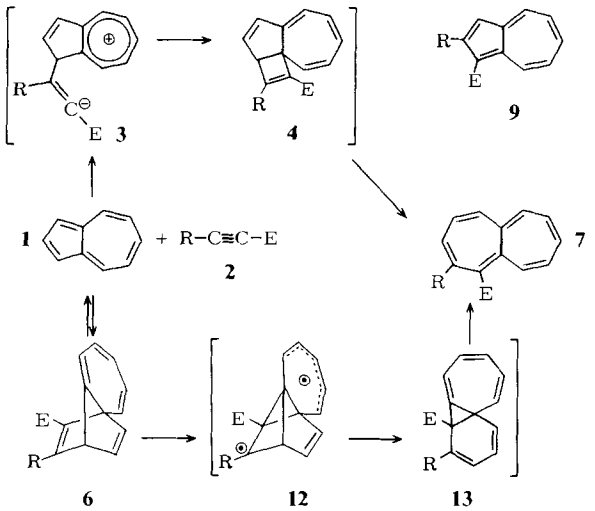
Cycloadditions of Azulene at High Pressure**

By *Frank-Gerrit Klärner**, *Barbara Dogan*, *Wolfgang R. Roth*, and *Klaus Hafner*

Dedicated to Professor William von E. Doering on the occasion of his 65th birthday

Reaction of dimethyl acetylenedicarboxylate **2a** with azulene **1** (boiling tetralin, 207.6 °C) leads to the heptalene-dicarboxylic acid dimethyl ester **7a**[1]. It was presumed that the intermediates **3a** and **4a** are involved. We have now established that high pressure (7 kbar) has an accelerating effect on this reaction and have also been able to isolate an intermediate from which the heptalene derivative **7a** is formed. This result makes it necessary to postulate a new mechanism. The addition of **2a** to **1** at 7 kbar occurs at 50 °C, at which temperature no reaction is observed at atmospheric pressure. After 67 h, apart from **7a** (11.7%) and **9a** (*ca.* 1%), the novel adduct **6a** (39.4%) was isolated (yields relative to reacted **1**; conversion: 19%).

Thermolysis of **6a** (0.09 M in [D_8]toluene, 60 °C, 1 bar, 30 h, conversion: *ca.* 55%) leads, *via* retro-cleavage, to **1** and **2a**, as well as to the heptalene diester **7a** (**1**:**7a** = 4.5). By means of control experiments it was established that under these conditions addition of **2a** to **1** does not occur (each 0.09 M in [D_8]toluene, 60 °C, 30 h). If **6a** is thermolyzed under pressure (0.09 M in toluene, 60 °C, 7 kbar, 30 h, conversion: *ca.* 51%), a greater amount of heptalene diester **7a** is formed (**1**:**7a** = 1.0); however, under these conditions addition of **2a** to **1** is observed (each 0.09 M in toluene, 60 °C, 7 kbar, 30 h, yield: **6a** (13%), **7a** (4%)).



a, R = CO_2CH_3; **b**, R = H
E = CO_2CH_3

1 also reacts with **2b** at 7 kbar and 70 °C to afford the adduct **6b**, although the reaction is very slow and the yield only moderate (*ca.* 1% after 66 h); neither yield nor conversion can be improved by increasing the temperature because at 150 °C the 1-azulene ester **9b** is now formed through cleavage of acetylene from **6b**. Thermolysis of **6b** at 80 °C, both at 7 kbar and at 1 bar (126 h, 70–80% conversion in each case) leads only to **1** and **2b**. In no case is the 1-heptalene ester **7b** formed.

These results cannot be accounted for by the reaction mechanism originally postulated. The intermediate **4a** is also not observed at 60 °C[7]. Apparently, **6a** is an intermediate on the route to the heptalene derivative **7a**. The question of whether the reversible reaction **1** + **2** ⇄ **6** proceeds *via* the dipolar intermediate **3** or by concerted [4+2]-cycloaddition[8] remains open. Here, the effect of pressure is less revealing. In both cases a strongly negative volume of activation is expected[9]. Since **6a** reacts 22 times faster than **6b** at 80 °C, we presume that a concerted Diels-Alder reaction occurs.

The different thermal behavior of **6a** and **6b** suggests the diradical intermediate **12a** is involved in the rearrangement **6a** → **7a**; **12a** is transformed into the norcaradiene **13a**, which can readily react further to **7a** *via* valence bond isomerization[10]. Formation of the diradical interme-

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diate can only compete with the retro Diels-Alder reaction if R is a radical-stabilizing substituent, as in **12a**.

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[7] The activation barrier for the rearrangement **4** → **7** could be very small. The disrotatory electrocyclic ring opening reaction **4** → 7, like that of bicyclo[4.2.0]octa-2,4,7-triene → 1,3,5,7-cyclooctatetraene, is orbital-symmetry allowed (E. Vogel, H. Kiefer, W. R. Roth, *Angew. Chem. 76* (1964) 432; *Angew. Chem. Int. Ed. Engl. 3* (1964) 442.

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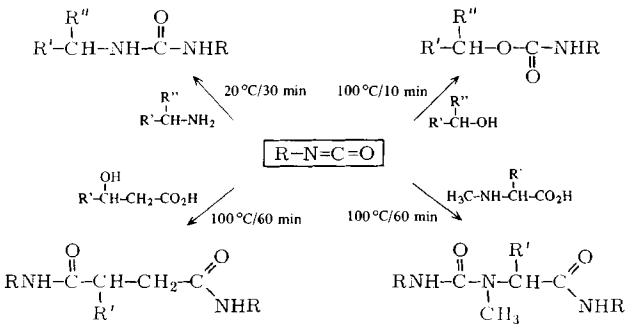
Isocyanates as Universal Reagents for the Formation of Derivatives for Gas Chromatographic Enantiomer Separation**

By *Ingrid Benecke* and *Wilfried A. König**

Hitherto, the formation of volatile derivatives for the gas chromatographic separation of enantiomers on chiral stationary phases required several different reaction steps, depending on the class of substance in question. We have now achieved this aim in only *one* step for some important classes of compounds by using isocyanates as reagents (Scheme 1). The separation effects, as obtained by the formation of diastereomeric association complexes between the chiral sample molecules and the chiral stationary phase, are considerably increased by the carbamate-, ureido- or amide-derivatives, which are obtained on reaction with isocyanates.

In this way the eight stereoisomers of menthol could be separated as *N*-isopropylcarbamates[8]. Chiral alcohols are



Scheme 1. (Selection) Reaction of isocyanates (R = CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, C_6H_5) with amines, secondary alcohols, β-hydroxycarboxylic acids and *N*-methylamino acids (R′ ≠ R″ = alkyl, aryl).

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of considerable importance in flavor and pheromone chemistry. For the first time β-hydroxy acids can now be separated as well as α-hydroxy acids[9]. Such acids frequently occur as natural metabolites or as chiral constituents of natural products. The formation of derivatives is simple: On heating *ca.* 0.1 mg of the sample for 1 h in isopropyl isocyanate and dichloromethane (1 : 2 v/v) the *N*-isopropyl-β-(*N*-isopropylcarbamoyloxy)alkane amides are readily obtained. The preparation of amides by heating carboxylic acids and isocyanates[11] has been known for some time but has never been used in microanalysis.

By analogy, the procedure mentioned here allows for the first time the preparation of derivatives of *N*-methylamino acids which are suitable for direct enantiomer separation. *N*-Methylamino acids frequently occur as constituents of peptide antibiotics and have gained increasing importance in peptide synthesis. Under the conditions described here the ureido derivatives are obtained in only *one* step. A racemization test for *N*-methylamino acids is of particular interest because of the strong tendency of such acids to undergo racemization during peptide coupling[14].

Chiral amines, which could be separated as *N*-trifluoroacetyl derivatives only on special stationary phases, readily form *N*-isopropylureido derivatives even at room temperature. They are separated with unusually high separation factors[9]. The same is true for α-branched amino acid derivatives and carboxylic acids.

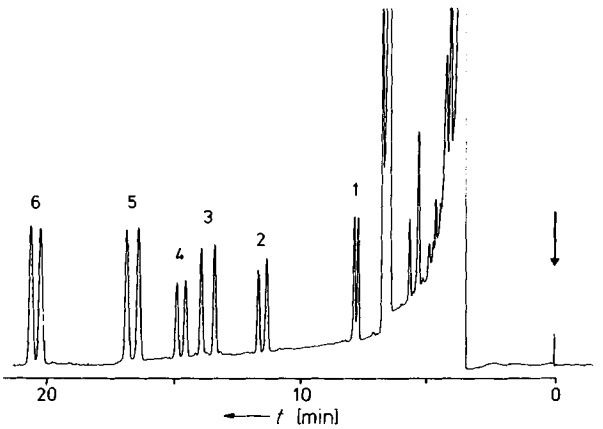

Fig. 2. Separation of racemic mixtures of 2-phenylbutanoic acid **1**, *S*-enantiomer = 2nd peak; lactic acid **2**, L-enantiomer = 2nd peak; 2-hydroxybutanoic acid **3**, L-enantiomer = 2nd peak; *N*-methylvaline **4**, D-enantiomer = 2nd peak; 2-amino-6-methylheptane **5**, no peak assignment; 3-hydroxybutanoic acid **6**, no peak assignment. Derivatives were obtained as shown in Scheme 1 by reaction with isopropyl isocyanate. Glass capillary (borosilicate glass, 40 m, 0.2 mm i.d.) coated with XE-60-L-valine-(*S*)-α-phenylethylamide [7], $T = 190\,^{\circ}C$ (Carlo Erba Model 2101 A gas chromatograph, carrier gas: 0.7 bar H_2).

The carbamate-, ureido-, and amide-derivatives, prepared with isopropyl isocyanate as universal reagent, are stable over months in solution; no racemization during formation of derivatives has been observed so far.

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[7] "Fused-silica" capillary columns with this phase are available form Chrompack, Middelburg (The Netherlands).

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Chemistry of Coal Utilization, Second Supplementary Volume. Edited by M. A. Elliot, Wiley-Interscience, New York 1981. 2374 pages, bound, $ 165.00.

The American "Chemistry of Coal Utilization", a handbook that has already become a classic and that is certainly unique in its scope and treatment of the material, has now been updated by the appearance of the second supplementary volume, after the original two-volume work of 1945, edited by *H. H. Lowry*, was first supplemented in 1963. As in the case of the previous volumes, a committee of the National Research Council of the U.S. National Academy of Sciences assumed the sponsorship of the new supplementary volume which, under the new editor *Elliot—Lowry* died ten years ago—includes contributions from 60 well-known authors. In continuation of the earlier work, detailed information is given not only on coal chemistry in the narrower sense but also, with the exception of mining technology, on all technologies for the utilization and upgrading of coal and on the conversion of coal into energy, fuels, and chemical raw materials. In spite of the primary aim to take up the story at the point at which the review of the first supplementary volume ended, *i.e.* essentially to give a critical review of the literature between about 1958 and the second half of the seventies and to describe further developments in this period, to a large extent the result has been an almost textbook-like account rather more suitable for advanced readers. Specifically, the 31 chapters deal with the coal industry, coal research and development (an overview written by the editor himself); coal resources (only the deposits of the United States are treated in detail); origin, petrography, and classification of coal; physical properties of coal and coal products; mechanical properties; plastic properties; analysis of coal, trace elements, and mineral constituents; chemical reactions and chemical constitution of coal; transport, storage, and handling; preparation; briquetting; pyrolysis and hydropyrolysis (3 chapters); solid pyrolysis products; coal tar (2 chapters); coke-oven gas; combustion of coal (2 chapters); coal ash—its effect on combustion; control of pollution from combustion processes; gasification of coal (3 Chapters); underground gasification of coal; liquefaction of coal (3 chapters); conversion of coal and coal gases into fuels, chemicals, and other products; and environmental health and safety implications of increased coal utilization.

On the whole, it must be said that the compilation and organization of the enormous volume of material has been highly successful. Overlapping between individual chapters, unavoidable because closely related subjects are treated by different authors, is kept to reasonable limits. The reviewer is not in a position to judge to what extent is has been possible to take into account the literature and all the developments of the various technologies. After all, the quality of the contribution depends in the final account on the knowledge, experience, and carefulness of the particular author (information about the professional career and the present position of each author is given by brief biographies at the beginning of the chapters). Apart from some contributions from the United Kingdom, Australia, and the German Federal Republic, the majority of the chapters have been written by American authors. In reading some chapters one cannot quite escape the (subjective) impression that the account, particularly of the economic and technical developments, is frequently limited substantially to the situation in the United States. For example, in Chapter 28 (Liquefaction Processes) all the American processes for direct liquefaction of coal are described in detail, whereas there is nothing about the corresponding developments of the National Coal Board in the United Kingdom and there are only a few lines on the "IG Nue Process" [*sic*] in Germany, by which is meant the new activities in connection with the hydrogenation of coal, based on the old IG process. A partial explanation for this shortcoming may be that these European developments really started up only in the mid-seventies, not long before the early editorial deadline (depending on the chapter, between August 1976 and the end of 1978). Other examples could be quoted. Another point of criticism relates to the use of units: it must be just as annoying for the English or American reader when, for example as on page 1782, temperatures are given in degrees Fahrenheit and enthalpies in Btu/lb-mole in one place and four pages later the same author uses Kelvin and kcal/g-mole!

The extensive subdivision of the text by heading makes for clarity, the graphic presentation including the figures and tables is excellent, and the citation of references in footnotes on the same page is exemplary. Small mistakes and printing errors do not appear to exceed the usual quota. The subject index, however, leaves something to be desired.

All in all, this second supplementary volume in combination with the earlier work offers a unique compilation, of inestimable value, of the scientific and technical literature on coal. No library should therefore delay in getting this supplement to their "Lowry". But even without the earlier volumes, which, by the way, can still be obtained as reprints, the book will be highly valuable for the interested specialists, if not indeed indispensable.

Matthias W. Haenel [NB 562 IE]

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Building Bridges Between Inorganic and Organic Chemistry (Nobel Lecture)**

By Roald Hoffmann*

Robert B. Woodward, a supreme patterner of chaos, was one of my teachers. I dedicate this lecture to him, for it is our collaboration on orbital symmetry conservation, the electronic factors which govern the course of chemical reactions, which is recognized by half of the 1981 Nobel Prize in Chemistry. From Woodward I learned much: the significance of the experimental stimulus to theory, the craft of constructing explanations, and the importance of aesthetics in science. I will try to show you how these characteristics of chemical theory may be applied to the construction of conceptual bridges between inorganic and organic chemistry.

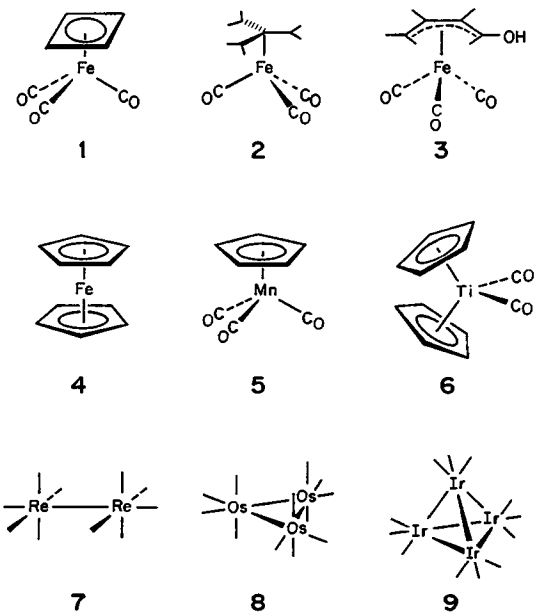
Fragments

Chains, rings, substituents—those are the building blocks of the marvelous edifice of modern organic chemistry. Any hydrocarbon may be constructed on paper from methyl groups (CH_3), methylenes (CH_2), methynes (CH), and carbon atoms (C). By substitution and the introduction of heteroatoms all of the skeletons and functional groupings imaginable, from ethane to tetrodotoxin, may be obtained.

The last thirty years have witnessed a remarkable renaissance of inorganic chemistry, and the particular flowering of the field of transition-metal organometallic chemistry. The complexes **1**—**9** are a selection of some of the simpler creations of the laboratory in this rich and ever-growing field.

Structures **1**—**3** illustrate at a glance one remarkable feature of transition-metal fragments. Here are three tricarbonyliron complexes of organic moieties—cyclobutadiene, trimethylenemethane, and 1-hydroxy-1,3-butadiene—which on their own would have little kinetic or thermodynamic stability. Yet complexed to $Fe(CO)_3$ these molecules are relatively stable: they exist in a bottle. The inorganic fragment is not merely a weakly attached innocent bystander: it transforms essentially and strongly the bonding relationships in the molecule.

Structures **4**—**6** contain the ubiquitous cyclopentadienyl ligand (Cp), two of them in the archetypical ferrocene, one in $CpMn(CO)_3$, two bent back in $Cp_2Ti(CO)_2$. Structures **7**—**9** introduce us to the simplest representatives of the



1 2 3 4 5 6 7 8 9

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burgeoning class of clusters—assemblages of two or more metal atoms embellished with external ligands.

If we seek order, unity, a way of thinking about these complexes, it is not difficult to perceive that the molecules contain as building blocks transition metal-ligand fragments, ML_n, such as $M(CO)_5$, $M(CO)_4$, $M(CO)_3$, or MCp. It must be said immediately that there is nothing special about the carbonyl ligand. It is merely a representative and common component of organometallic complexes. Phosphanes, olefins, alkyls will do as well.

To reconstruct the complexes **1**—**9**, we need to know the electronic structure of the fragments. For the simple qualitative picture of the bonding in these molecules that we seek, we do not need to know every last detail of the electronic structure of each molecule. It will suffice that we know the frontier orbitals of the fragments—the higher occupied and the lower unoccupied levels—in other words the valence active orbitals of each fragment. It is *Kenichi Fukui* who taught us the importance of the frontier orbitals. We shall soon see that it is the resemblance of the frontier orbitals of inorganic and organic moieties that will provide the bridge that we seek between the subfields of our science.

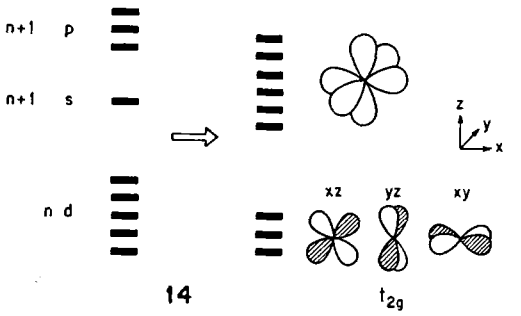
Over the last eight years my coworkers and I have built up a library of the orbitals of ML_n fragments[1-3]. We have done so using entirely qualitative, approximate molecular orbital calculations of the extended Hückel type (a procedure for its time, developed with another of my teachers, *William N. Lipscomb*) and symmetry arguments (the value of which I first learned from still another of my teachers, *Martin P. Gouterman*). Molecular orbital theory, *Robert S. Mulliken*'s great contribution to chemistry, is fundamental to our approach, be it in the construction of the very orbitals of the fragments, their changes on molecular deformation, or the interaction of several such fragments to restore the composite molecule. Yet when I seek the simplest of all possible ways to tell you of the orbitals of these fragments, I am led back to the valence bond picture introduced into chemistry by *Linus Pauling*[4].

Let us go back to the building blocks. The general fragments ML_n, **10**—**13**, may be viewed in many ways. One convenient approach is to consider them as pieces of an octahedron.

10 **11** **12** **13**

This is quite analogous to perceiving CH_3, CH_2, and CH in a tetrahedron. If not a unique viewpoint, it is a useful one. Given that we have an octahedron, or pieces thereof, let us prepare the metal atom for octahedral bonding, and then introduce the appropriate number of ligands.

The valence orbitals of the transition metals are nd, (n+1)s and (n+1)p, with n=3, 4, 5. To prepare the metal atom for bonding we must form six equivalent octahedral hybrids. This is accomplished (cf. **14**), by using all of the s and p functions and two of the d's. Three d functions, d_{xz}, d_{xy}, and d_{yz}, are left unhybridized. They may be described as the t_{2g} set of the crystal field, ligand field, or molecular orbital theories of an octahedral complex[5].



14 t_{2g}

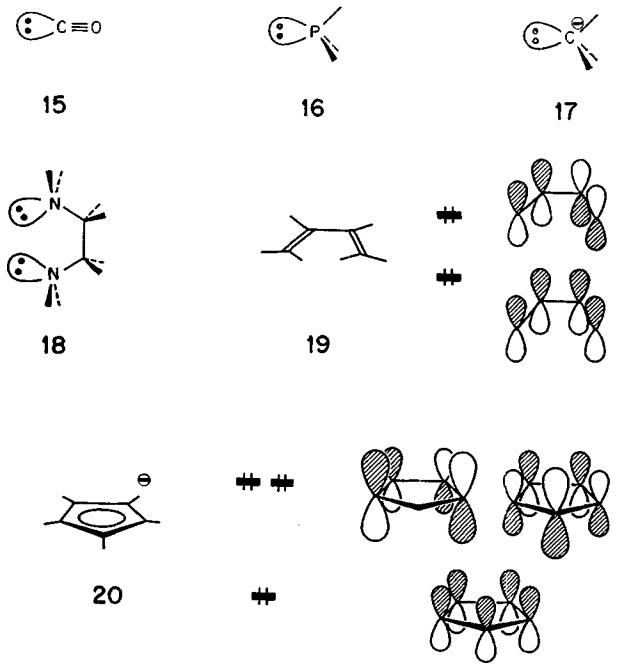
To form an octahedral complex we would introduce six ligands to make use of the six octahedral hybrids. Perhaps it is appropriate to digress here and make clear our ligand convention, which is to consider the ligand always as an even-electron Lewis base. While acceptor character or Lewis acidity is a desirable feature in a ligand, Lewis basicity or donation is essential. We see the basicity in the form of the lone pairs of CO, PH_3, and CH_3^- (**15**—**17**), in bidentate four-electron ligands, be they ethylenediamine (**18**) or butadiene (**19**), or in the electronically tridentate $C_5H_5^-$ (Cp^-, **20**), the equivalent of three two-electron bases[6].

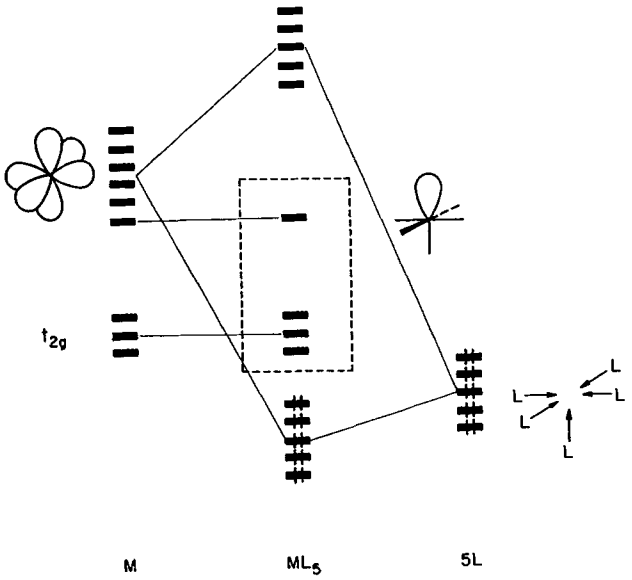
Let six two-electron ligands approach the metal atom prepared for octahedral bonding (cf. **21**). Sizable σ overlaps lead to formation of strongly metal-ligand σ bonding combinations, and their strongly metal-ligand σ* antibonding counterparts. The six electron pairs of the ligands enter the six bonding combinations. Any electrons the metal contributes enter the t_{2g} orbital left behind. Indeed, for $Cr(CO)_6$ with its 6 metal electrons we attain a nice closed shell configuration, a situation we have learned to associate with relative kinetic and thermodynamic stability in organic chemistry.

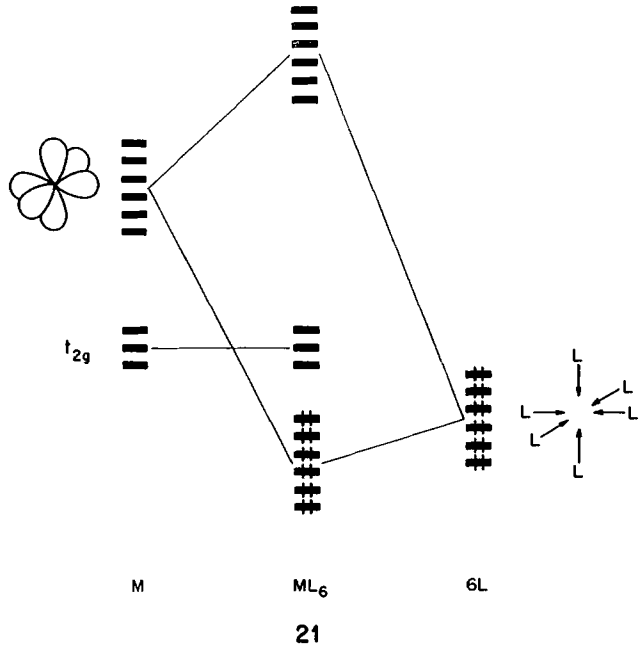
What if we have not six ligands coming in, but only five? This situation is depicted in **22**. Five hybrids interact strongly, are removed from the frontier orbital region, just as all six were in **21**. One hybrid, the one pointing toward where no ligand is, remains roughly untouched, relatively low-lying in energy. The frontier orbitals, enclosed in a dashed box in **22**, now contain the t_{2g} set plus one hybrid.

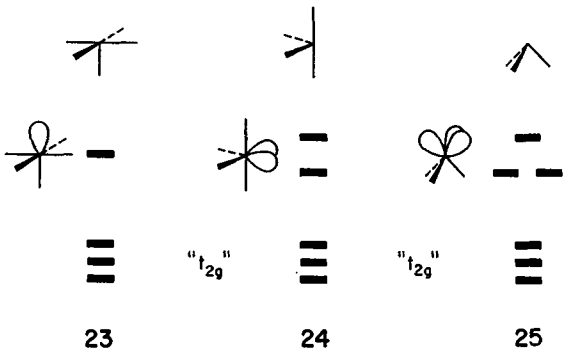
What if we have four ligands (ML_4) or three (ML_3)? Much the same thing happens. In ML_4 two hybrids are left behind, in ML_3 three. We have thus reached the simplest of all possible pictures of the electronic structure of the ML_n fragments with n=5, 4, 3, namely that given in **23**—**25**. The ML_n fragment's frontier orbitals consist of the descendants of an octahedral t_{2g} set at relatively low energy, and above them 6−n (one for n=5, two for n=4, three for n=3) hybrids pointing toward the missing octahedral vertices.

What remains is to decide how many electrons to place into these frontier orbitals, and here the ever-useful Mendeleev Table, modified in **26** for electron counting purposes, tells us that Fe in oxidation state zero will have eight electrons in $Fe(CO)_4$ or $Fe(CO)_3$, and so will Co^I or Ni^{II}.









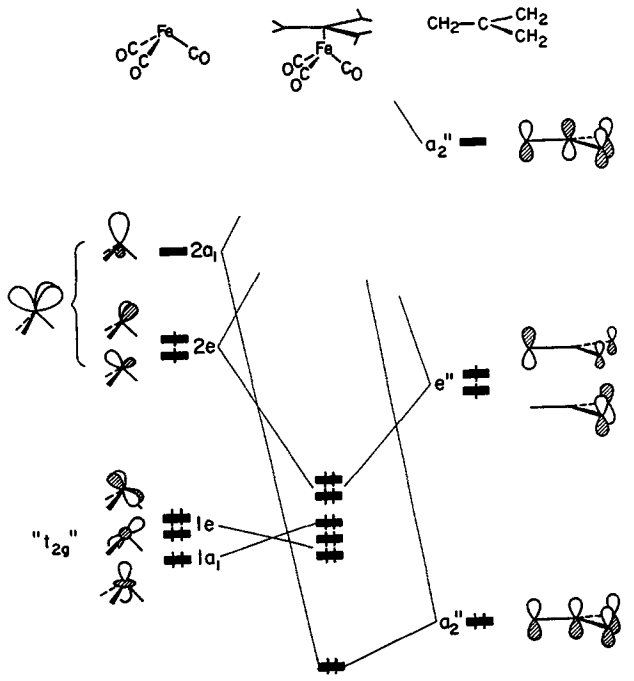
4	5	6	7	8	9	10
Ti	V	Cr	Mn	Fe	Co	Ni
Zr	Nb	Mo	Tc	Ru	Rh	Pd
Hf	Ta	W	Re	Os	Ir	Pt

26

The reader had best beware. The account given here is simplified, as much as I dare simplify it. In that process, perforce, is lost the beautiful detail and complexity that makes $Fe(CO)_3$ different from $FeCl_3^{3-}$. There is a time for detail and there is a time for generality. The reader of my papers will know that my coworkers and I do not stint on detail, whether it is in explication or in perusal of the literature. But the time now, here, is for building conceptual frameworks and so similarity and unity take temporary precedence over difference and diversity.

Recall that the reason for building up the frontier orbitals of inorganic fragments is that we wish to use these orbitals in the construction of organometallic and inorganic complexes. We are now ready for that task. For instance, if we want tricarbonyl(trimethylenemethane)iron we construct a molecular orbital interaction diagram (cf. 27). On one side are the orbitals of $Fe(CO)_3$ just discussed, on the other side the older, better known frontier orbitals of $C(CH_2)_3$. We interact the two, using the full armament of group theory and perturbation theory[7] to follow what happens.

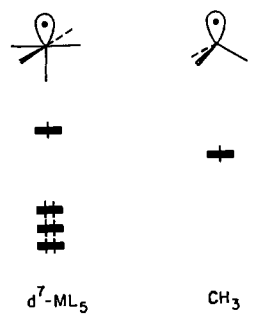
I will not trace this argument any further, for the primary purpose of this lecture is not the description of the electronic structure of organometallic complexes. My coworkers and I have done this comprehensively elsewhere[1,8]. Instead, I wish to describe a bridge between organic and inorganic chemistry that becomes possible the moment we gain knowledge of the orbitals of the ML_n fragments.



27

The Isolobal Analogy

Consider the d^7-fragment, $Mn(CO)_5$ (or $Co(CN)_5^{3-}$). Above the three lone pairs in the t_{2g} set this doublet molecule has a single electron in a hybrid pointing away from the ML_5. The similarity to CH_3, the methyl radical, is obvious (cf. **28**).



28

The representation **28** is, of course, schematic. Figure 1 shows the a_1 orbitals of MnH_5^{5-} and CH_3, so as to provide a more realistic comparison.

If d^7-ML_5 is like CH_3 then they should both behave similarly. Let us think about what a methyl radical does. It dimerizes to ethane and starts radical chains. $Mn(CO)_5$ or $Co(CN)_5^{3-}$ do similar things. They dimerize to $Mn_2(CO)_{10}$ or $Co_2(CN)_{10}^{6-}$ (cf. **29**), and each has a rich radical-type chemistry[9]. One can even codimerize the organic and inorganic fragments to give $(CO)_5MnCH_3$. That may not be the preferred way to make this quite normal organometallic alkyl complex in the laboratory, but the construction on paper is quite permissible.

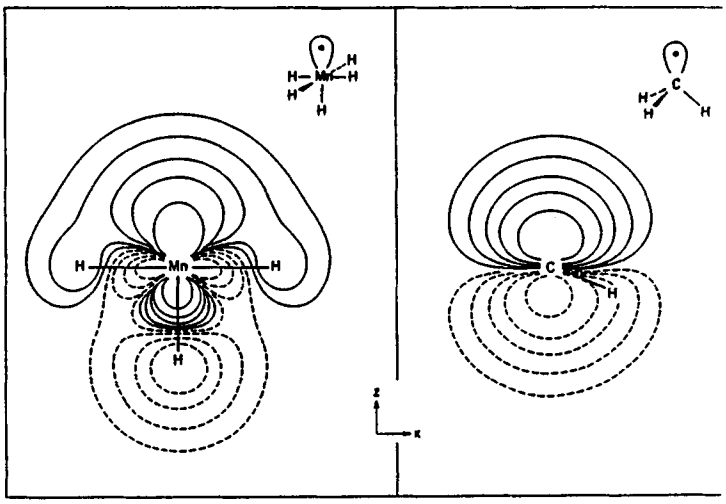
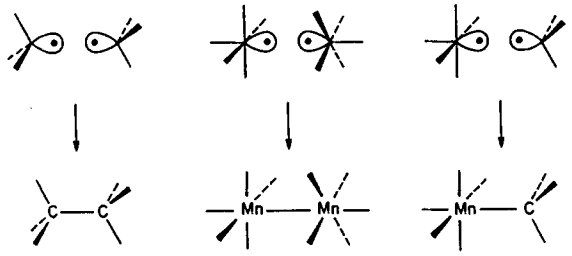


Fig. 1. Contour diagram of the isolobal a_1 orbitals of MnH_5^{5-} (left) and CH_3 (right), as computed by the extended Hückel method. The contours of Ψ, plotted in a plane passing through Mn and three H's (left) and C and one H (right), are ± 0.2, ± 0.1, ± 0.055, ± 0.025, ± 0.01.



29

CH_3 and d^7-ML_5 resemble each other. Another way we can see that resemblance, traceable to their singly occupied a_1 orbitals, is to compare the overlap of both orbitals with a probe ligand, let us say a hydrogen atom. This is done in Figure 2. Note the remarkable parallelism of the two overlaps. The H—CH_3 overlap is everywhere smaller than the H—MnL_5 overlap, but the dependence of both on the distance is quite similar.

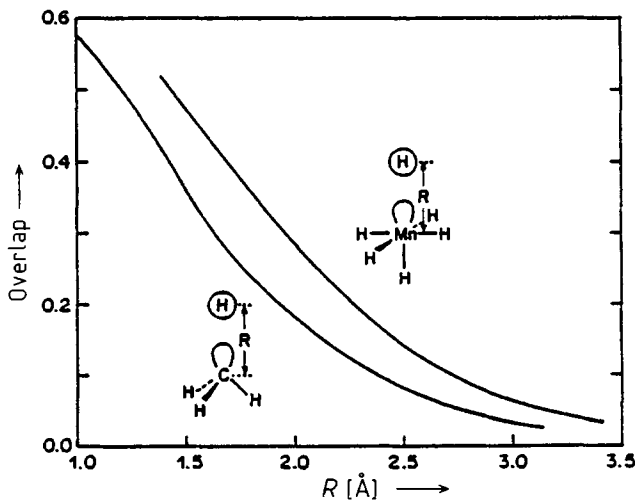


Fig. 2. Overlap integrals between the a_1 frontier orbital of MnH_5^{5-} and CH_3 and a H 1s orbital at a distance R from the Mn or c atom.

A word is needed to describe the resemblance of the two fragments, CH_3 and d^7-ML_5. They are certainly not isostructural, nor are they isoelectronic. However, both possess a frontier orbital which looks approximately the same for the two fragments. We will call two fragments *isolobal* if the number, symmetry properties, approximate energy and shape of the frontier orbitals and the number of electrons in them are similar—not identical, but similar[10]. Thus CH_3 is isolobal with $Mn(CO)_5$. We will introduce a symbol for the isolobal relationship: a "two-headed" arrow with half an orbital below. Thus,

$CH_3 \leftrightarrow Mn(CO)_5$

Let's extend the definition a little:

1) If $Mn(CO)_5$ is isolobal with CH_3, so are $Tc(CO)_5$ and $Re(CO)_5$, as well as $Fe(CO)_5^+$. The shape of the a_1 hybrid will vary slightly with different principal quantum numbers, but essentially it is only the d-electron count that matters.

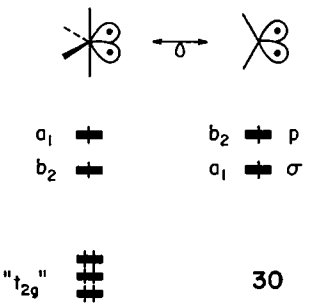
2) If $Mn(CO)_5$ is isolobal with CH_3, then $Cr(CO)_5$, $Mo(CO)_5$ or $W(CO)_5$ are isolobal with CH_3^+, and $Fe(CO)_5$ (square pyramidal!) is isolobal with CH_3^-.

3) If $Mn(CO)_5$ is isolobal with CH_3, so are $Mn(PR_3)_5$ or $MnCl_5^{2-}$ or any d^7-ML_5 species. And so is $CpFe(CO)_2$, a ubiquitous fragment. The procedure here is to write $CpFe(CO)_2$ as $Cp^-Fe^+(CO)_2$, and to replace the Cp^- by its isolobal equivalent of three carbonyls, reaching $Fe(CO)_5^+$, which is isoelectronic with $Mn(CO)_5$.

Let us go on to the ML_4 fragment. It is clear that a d^8-ML_4 species, *e.g.* $Fe(CO)_4$, is isolobal with a methylene or (carbene, CH_2).

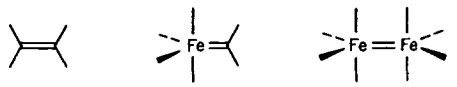
$Fe(CO)_4 \leftrightarrow CH_2$

As **30** reveals, both fragments have two electrons in delocalized a_1 and b_2 orbitals which are the equivalent of two localized hybrids. There are explicable differences in the ordering of the two combinations[11]. The different ordering has, however, no grave consequences—recall that we are not so much interested in the fragments themselves as in their bonding capabilities. The moment we interact $Fe(CO)_4$ or CH_2 with another ligand, the initial ordering of a_1 and b_2 becomes relatively unimportant since both are typically strongly involved in the bonding.



30

Dimerize, conceptually, the isolobal fragments $Fe(CO)_4$ and CH_2. One gets the known ethylene, **31**, the tetracarbonyliron carbene complex, **32**, derivatives of which are known[12], and $Fe_2(CO)_8$, **33**. The last molecule is unstable, and so far has been observed only in a matrix[13]. We come here to a cautionary note on the isolobal analogy. The isolobal analogy carries one between organic and inorganic molecules of similar electronic structure. But there is no guarantee that the result of such an isolobal mapping (**31** $\leftrightarrow$ **33**) leads one to a molecule of great kinetic stability. It might, or it might not.

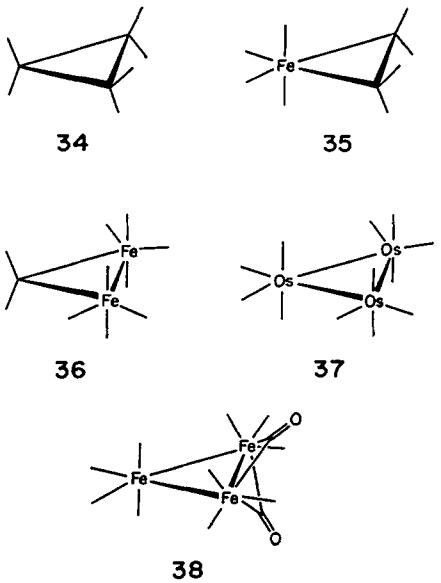


31 **32** **33**

Lest the reader be concerned about this limitation of the analogy let me remind him or her of what happens as one proceeds from ethylene down Group IV. Si, Ge, Sn, Pb substitution leads to olefin analogues, but they are kinetically and thermodynamically so unstable that it has taken great effort to provide evidence for their fleeting existence.

$Fe_2(CO)_8$, **33**, has π and π^* levels similar to those of ethylene. But the low energy of its π^* makes this molecule coordinatively unsaturated. It can, for instance, add another CO to reach the stable enneacarbonyldiiron. More interesting, as we will soon see, is the strategy of stabilizing the unstable $Fe_2(CO)_8$ by making a complex of it, just as is routinely done for unstable organic molecules (**1**—**3**).

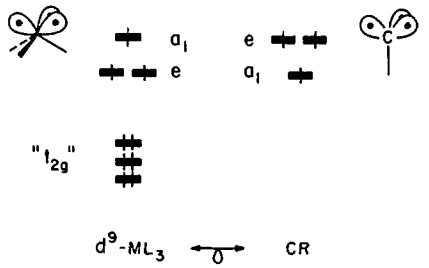
$Fe(CO)_4$, $Ru(CO)_4$, or $Os(CO)_4$ may be trimerized in various combinations with methylene, as in **34**—**37**. These cyclopropanes, ranging from all-organic to all-inorganic, are known. But note that when I show the "all-metallic" three-membered ring I have to go to Os. It is well known that the ground state structure of $Fe_3(CO)_{12}$ is **38**, with two bridging carbonyls[14]. Another limitation of the isolobal analogy is exposed here: the unbridged Fe structure analogous to **37** is certainly not much higher in energy than **38**, but nevertheless the lowest energy structure is bridged. Movement of some ligands (*e.g.* carbonyls, but not phosphanes) in and out of bridging sites is an experimental reality, a facile process, for transition metal complexes, especially of



34 **35** **36** **37** **38**

the first transition series. Such easy terminal to bridging interconversions are rare in organic chemistry, with the exception of carbonium ions. Bridging in inorganic structures, when it does occur, does not cause a major perturbation in the nature of the frontier orbitals.

Consider next the d^9-ML_3 fragment, *e.g.* $Co(CO)_3$. This is isolobal with a methylidyne (or carbyne) CH, as shown in **39**. Once again there are differences, though of no great



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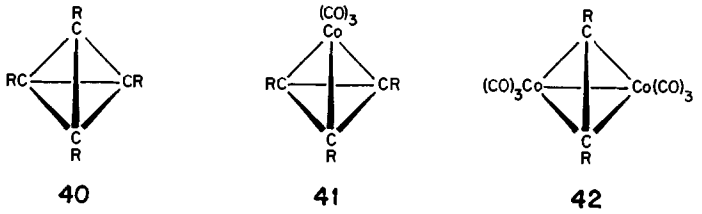
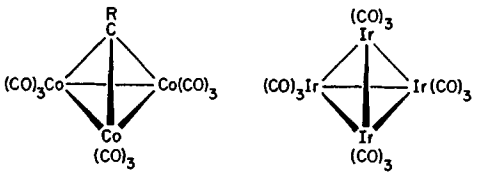
significance, in the a_1 versus e energy ordering between the two fragments. Their similarity is revealed most strikingly by the existence of the entire series of mixed organic and inorganic tetrahedranes, **40**—**44**. To be sure, **41** can be



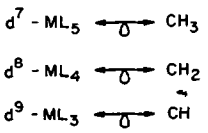
40 **41** **42**



43 **44**

called a cyclopropenyl complex and **42** a binuclear acetylene complex, but I believe something is gained in seeing the entire series as a progression of isolobal substitution.

The fundamentals of the isolobal analogy have now been exposed. Just how far-reaching the relationships written here



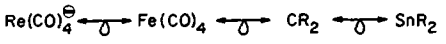
are, will become clearer shortly. For the moment it is important to note that the isolobal analogy is not solely the creation of my research group. In his fruitful explorations of the reactivity of d^8-square planar complexes *Halpern* often made use of the similarity of such an ML_4 entity to a carbene[9a]. He did the same for d^7-ML_5 and organic free radicals[9a]. *Dahl*, in a beautiful series of structural studies of transition metal clusters, saw clearly the relationship of the orbitals of an ML_n fragment to a chalcogen or pnicogen atom, which of course are easily related to CR[15,16]. And most importantly, *Wade*[17] and *Mingos*[18] independently developed a comprehensive and elegant picture of the electronic structure of transition- metal clusters by relating them to the polyhedral boron hydrides (which *Lipscomb* and I studied—the circle closes!). It is a trivial step from BH to CH^+. All of these workers saw the essence of the isolobal analogy.

Structural Implications of the Isolobal Analogy

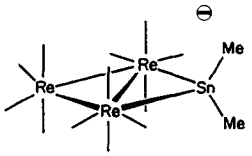
How quickly the hands and mind of man provide us with the problem of choice! The molecules I would need to illustrate the isolobal analogy at work did not exist thirty years ago. Now they are around us, in superabundance. I have made a selection, based in part on the ease with which these lovely molecules illustrate the principles, in part on the ambiguous and ephemeral basis of recent (1981) appearance in the literature.

One obvious use of the isolobal analogy is in the structural sense. The analogy allows us to see the simple essence of seemingly complex structures. I should like to show you some examples centering on the ML_4 fragment.

Last year there appeared a structure of the cluster $HRe_3(CO)_{12}Sn(CH_3)_2$ from the work of *Kaesz et al.*[19]. The unique hydrogen was not located; presumably it bridges one Re—Re bond. If we remove the hydrogen as a proton, a convention we have found useful[8n], we reach $Re_3(CO)_{12}Sn(CH_3)_2^-$, **45**. Not a usual molecule, but the isolobal chain



allows us immediately to see the very close similarity of this structure to the previously known **46**[20] and **47**[21].



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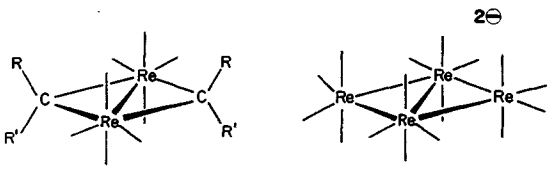
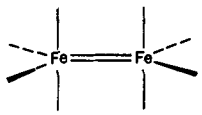


46 **47**

It is interesting to speculate when we might see the missing members of the series on the organic side, $(CO)_4Re(CH_2)_3^+$ and $(CH_2)_4^{2+}$.

Two ML_4 fragments united yield the aforementioned unstable $Fe_2(CO)_8$ system, **48**. It was hinted before that one should think of stabilizing this species by complexation. A pretty example is at hand, **49**[22]. Two $Fe_2(CO)_8$ units are complexed by a tin atom! Note the pinning back of the



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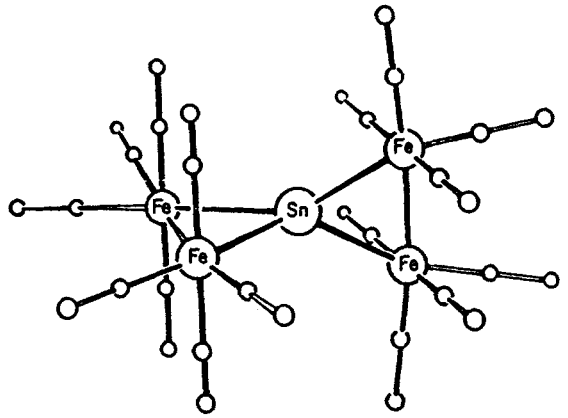
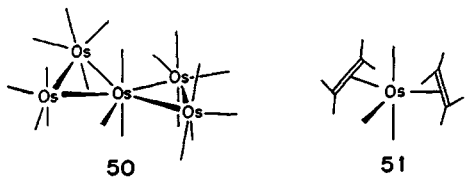
equatorial carbonyls, analogous to the bending back of hydrogens in a transition metal complexed olefin. Alternatively, and interestingly, this can be considered as a spiropentane.



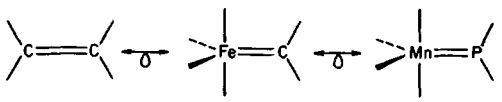
49

Earlier last year, *Lewis, Johnson et al.* published a synthesis and structure of $Os_5(CO)_{19}$[23]. The structure, **50**, appears terribly complicated until one realizes it is really **51**, a typical trigonal bipyramidal $Os(CO)_5$ derivative, with two of the equatorial carbonyls substituted by olefins, or rather by the $Os_2(CO)_8$ olefin analogues. The "olefin" orientation is just as it should be[1k,o].



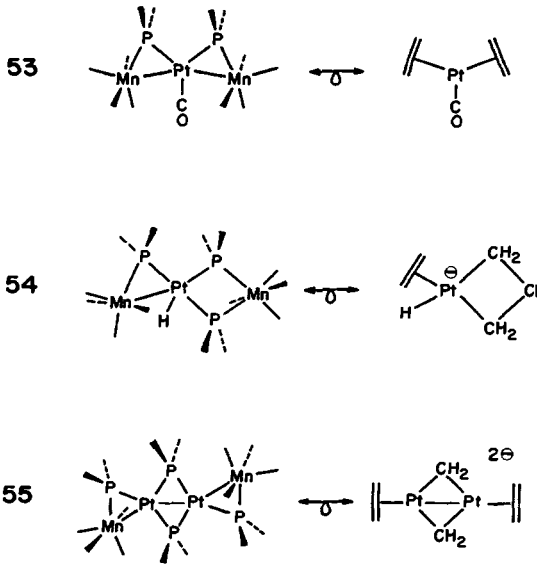
50 51

Another system isolobal to ethylene and $Fe_2(CO)_8$ is the "mixed dimer" $(CO)_4FeCH_2$. Upon formally shifting an electron from the metal to the carbon, a bit of alchemy, one gets to a phosphido complex **52**:



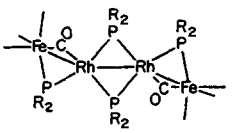
52

The reason for this transformation sequence is that complexes of $Mn(CO)_4PR_2$ have been made. *Braunstein, Grandjean et al.* have reported a remarkable set of structures, among them the three shown with their isolobal analogues in **53**—**55**[24]. In each structure we can see the obvious ethylene-like $(CO)_4MnPR_2$ entity.



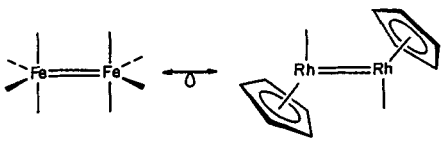
53 54 55

At the same time that these structures were published there appeared a structure of **56**, synthesized in an entirely different way by *Haines, Steen,* and *English*[25]. Unbridge the two semibridged carbonyls, do a bit more electronic alchemy relating Mn—Pt to Fe—Rh, and the relationship to **55** becomes crystal clear.



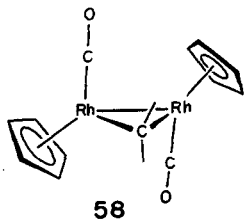
56

Realizing that $Fe(CO)_4 \leftrightarrow CpFe(CO)^- \leftrightarrow CpRhCO$, we see immediately that **57** is yet another $Fe_2(CO)_8$ analogue.



57

Thus, the methylene complex, **58**, synthesized by *Herrmann* is a two-thirds inorganic cyclopropane[26].

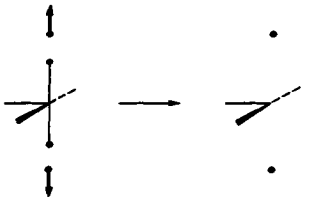


58

There are a few more fascinating $Cp_2Rh_2(CO)_2$ structures to be shown, but first we need to examine one extension of the isolobal concept.

The Relationship between ML_n and ML_{n-2} Fragments

Earlier in the discussion we looked at two octahedral fragments, ML_5 and ML_4, in which a pair of axial ligands remained. If we remove these ligands (cf. **59**) an interesting extension of the isolobal analogy emerges.



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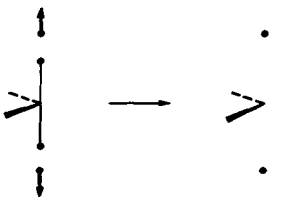
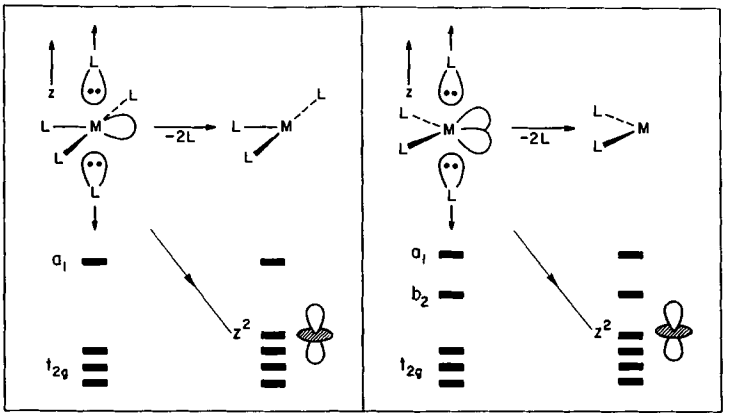
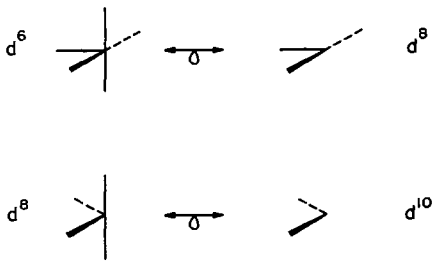


If the z-axis is oriented along the direction of the vanishing ligands, then it is clear that the main result of this perturbation is that the metal d_{z^2} atomic orbital is lowered in energy. It returns from the metal-ligand σ-antibonding manifold to become a non-bonding orbital (cf. **60**, **61**)[10a, 3c].



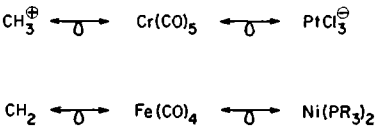
60 **61**

The high-lying orbitals (one in ML_5, two in ML_4) remain[27]. The obvious relationships that emerge then are those between a d^n-ML_5 and a d^{n+2}(C_{2v})- or T-shaped ML_3; and between d^n(C_{2v})-ML_4 and d^{n+2}-ML_2. Or to put it explicitly in terms of the most common fragments, **62**.



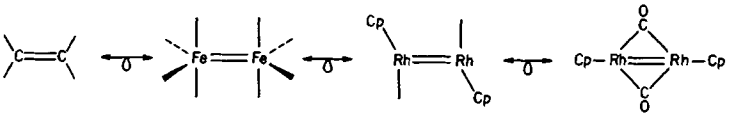
62

So we now add some further diversity to the non-isolobal mapping which is the isolobal relationship:



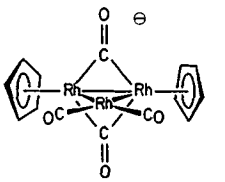
An obvious application is to olefin complexes; the similarity of $(CO)_4Fe(C_2H_4)$ to $(PR_3)_2Ni(C_2H_4)$, and that of $(CO)_5Cr(C_2H_4)$ to Zeise's salt emerges directly[10a, x].

Returning to the $[CpRh(CO)]_2$ analogue of ethylene, we can now think about some other structures. First, it turns out that moving the carbonyl groups into the bridge does little to change the ethylene-like nature of the dirhodium fragment, **63**[11a].



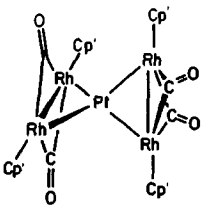
63

Since $CH_2 \leftarrow\!\!\rightarrow Fe(CO)_4 \leftarrow\!\!\rightarrow Pt(CO)_2 \leftarrow\!\!\rightarrow Rh(CO)_2^-$, it is possible to see in the compound of *Bergman et al.*, **64**[28], an analogue of *Herrmann*'s compound **58**.



64

Essentially the same fragment, **63**, reappears in the fantastic $[CpRh(CO)]_4Pt$ structure, **65**, of *Stone et al.*[29] ($Cp = \eta^5$-C_5Me_5) and can be related to the $(RC{\equiv}CR)_2Pt$ structure, **66**, earlier synthesized by the same group[30].



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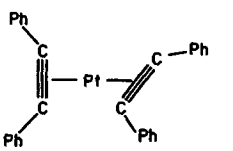
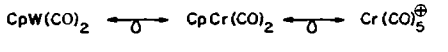


66

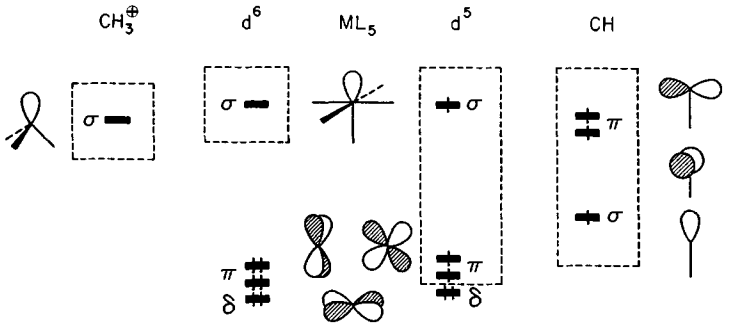
Into the t_{2g} Shell

It turns out that not only is d^9-$Co(CO)_3$ isolobal with CH, but so is d^5-$CpW(CO)_2$. To see how this comes about let us first relate the Cp complex to a simple ML_n.



As was shown earlier, $Cr(CO)_5^+$ is isolobal with CH_3^{2+}. That is not a very productive analogy. So let us examine

$Cr(CO)_5^+$ in more detail. The electronic structure of an ML_5 fragment was given earlier. It is repeated in more detail on the left of **67**. The ML_5–CH_3 analogy concentrates on the hybrid of $\sigma(a_1)$ symmetry. But the t_{2g} set, even if it is less "directional" than the hybrids, has extent in space and well-defined symmetry properties. In particular, two of the t_{2g} orbitals are of π pseudosymmetry, one of δ-type. If, as we are forced to by the electron deficiency, we extend our view at least to the π component of the t_{2g} set (dotted lines at right in **67**), we see a clear relationship between d^5-ML_5 and CH, just as there is between d^7-ML_5 and CH_3.



67

A little further reflection will show that by using one half of the π set of the t_{2g} we can get a relationship between d^6-ML_5 and CH_2.

To summarize:

d^7-ML_5 ⟷ CH_3

d^6-ML_5 ⟷ CH_2

d^5-ML_5 ⟷ CH

or to put it another way

d^6-ML_5 ⟷ $CH_3^\oplus$

d^6-ML_5 ⟷ CH_2

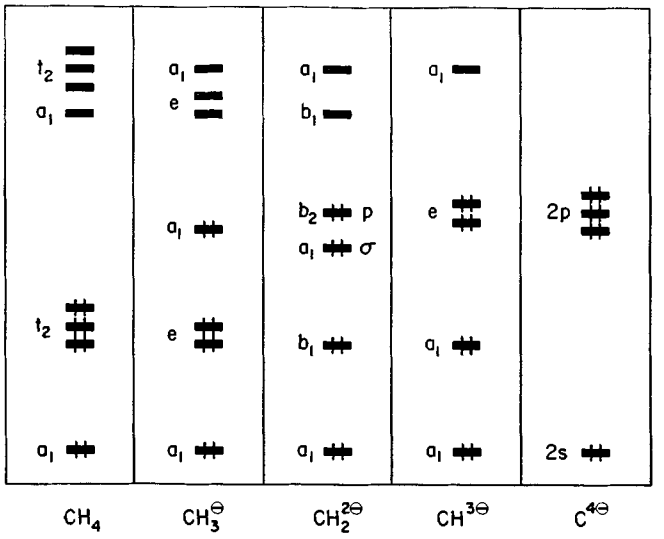
d^6-ML_5 ⟷ $CH^\ominus$

This gives us another way of looking at things, a *deprotonation analogy*. In what way is CH_3^+ like CH_2 or CH^-? Let us draw out their orbitals schematically, including CH_4 for good measure, in **68**.

Taking away a proton from each molecular fragment does not change its ability to function as a donor (though its quality or donor strength will be *very* different). Each fragment, from CH_4 to C^{4-}, is in principle an eight-electron donor.

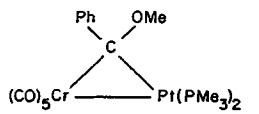
To recapitulate: the isolobal analogy is not a one-to-one mapping. A d^6-ML_5 fragment is isolobal with CH_3^+, CH_2, and CH^-. This is why the d^5-$CpW(CO)_2$ is isolobal with CH.

The isolobal analogy for low d-electron count metals has been exploited most notably in the work of *Stone*'s group at Bristol. Just four compounds from their many beautiful examples are shown in **69**–**72**[31].



68

Since d^6-$Cr(CO)_5$ ⟷ CH_2 ⟷ d^{10}-$Pt(PR_3)_2$, **69** corresponds to cyclopropane. Since $CpW(CO)_2$ is isolobal with CR, **70** corresponds to cyclopropene. Both isomers **71** and **72** are related to $(CO)_3Fe$(cyclobutadiene), **1**, or for that matter to the organic square-pyramidal $C_5H_5^+$[32].



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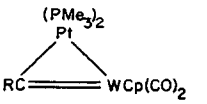

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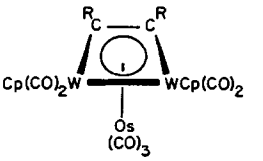

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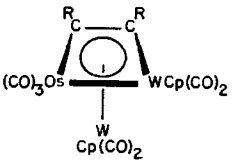
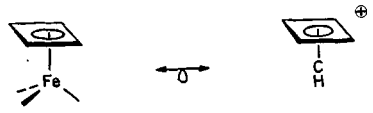


72

From Inorganic to Organic Chemistry

The psychological direction of the isolobal analogy in general has been to make one feel more comfortable about the structures of complex inorganic molecules by relating them to known, presumably simpler, organic molecules. It is interesting to reverse this process and think about as yet unsynthesized organic structures related to known inorganic ones. The mapping from one realm of chemistry to the other must be accompanied by the warning already given: there is no guarantee that the "product" of an isolobal transformation is as stable, kinetically or thermodynamically, as the "reactant"[33].

$Fe(CO)_3$ is isolobal with CH^+. Thus, **1** is related to $C_5H_5^+$, **73**[32], and the ubiquitous ferroles, **74**[34], are related to $C_6R_6^{2+}$, **75**[35]. Another product of the interaction of acetylenes with carbonyliron species is the "flyover bridge" molecule, **76**, a binuclear ring-opened fulvene complex[34]. The isolobal replacement carries over to **77**.



1 73

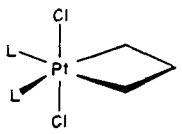
74 75

This is an unusual hydrocarbon $C_8H_8^{2+}$ of C_2 symmetry, a hypothetical doubly homoallylic cation. It is not a geometry one would normally have thought of for a heptafulvene dication, yet once reached by the isolobal mapping it appears to be geometrically reasonable[36]. More mappings of this type await exploitation.

76 77

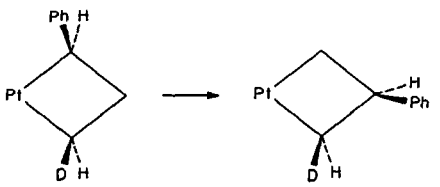
From Organic to Inorganic Reaction Mechanisms

Puddephatt, Tipper et al.[37] have discovered a remarkable rearrangement of a platinacyclobutane, **78**, in which a carbon atom adjacent to the metal, with its substituents,



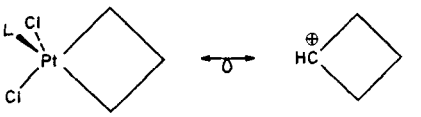
78

exchanges in a very specific way with the carbon atom opposite the metal[37]. The labeling experiment of *Casey et al.* showing this phenomenon most directly is given in **79**[38]. How does this happen?



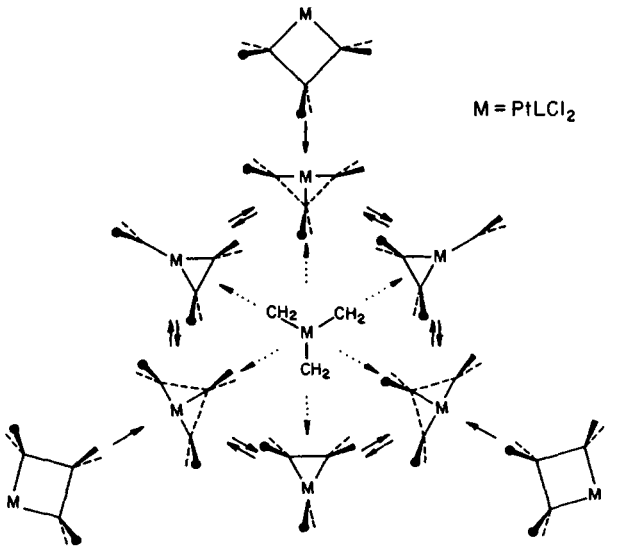
79

Kinetic evidence for a primary dissociative step to $Cl_2(py)Pt(CH_2)_3$ exists[37]. Suppose the ML_3 fragment can distort from its original T-shape to a C_{3v} geometry. Since d^8-$PtCl_2(py)$ is isolobal with CH^+, we can see a relationship to the cyclobutyl cation, **80**.



80

This association immediately brings to mind the entire complex of speculations and facts surrounding the facile rearrangement of cyclobutyl cations through "bicyclobutonium" waypoints[39]. The motions likely to occur are shown in **81**. Ligand loss is followed by geometric reorganization at the metal, approach to a "bicyclobutonium structure", an itinerary around the periphery of a Jahn-Teller wheel through "cyclopropyl carbinyl" waypoints, and exit through an isomeric "bicyclobutonium" structure.



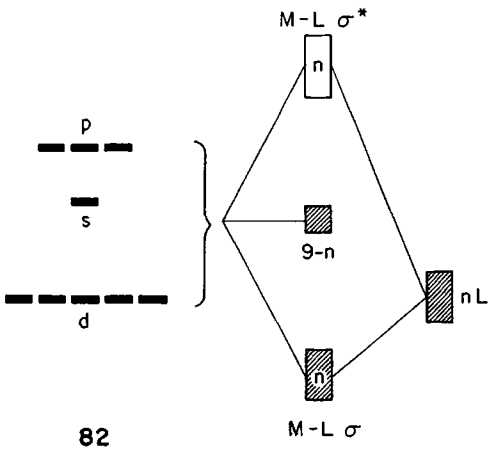
81

This is but one instance among many where the isolobal analogy is useful in moving between organic and inorganic reaction mechanisms.

Beyond the Octahedron

The octahedron was a most useful starting point for generating fragment frontier orbitals, thereby engendering the isolobal analogy. But the octahedral polytype is not unique for six-coordinate complexes, and higher coordination numbers are feasible. We seek another more far-ranging derivation and find one based on the 18-electron rule.

An (unoriginal) justification of this rule goes as follows: Consider n ligands, $n \leq 9$, approaching a metal with its 9 valence orbitals (cf. **82**). A little group theory shows that for the octahedron and most, but not quite all, coordination geometries the n ligand orbitals will find a match in number, symmetry properties, and extent in space among the hybrid sets that can be formed from the nine metal orbitals. The exceptions are very well understood[40]. Given this match, n M—L σ bonding combinations will go down in energy, n M—L σ^* antibonding combinations will go up, and $9-n$ metal orbitals will remain relatively un-

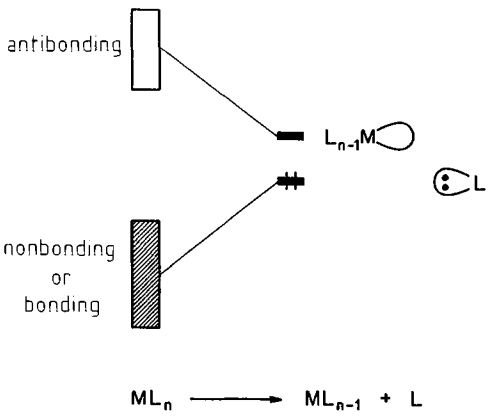


82

touched, approximately non-bonding. The 18-electron rule then is the statement: "Thou shalt not fill antibonding orbitals". Filling bonding (n)+nonbonding (9−n) orbitals leads to 9 electron pairs or 18 electrons.

This "proof" is trivial but not silly. Upon a little reflection it will lay bare the limitations of the 18-electron rule on the left and right side of the transition series, for special symmetry cases, and for weak field ligands.

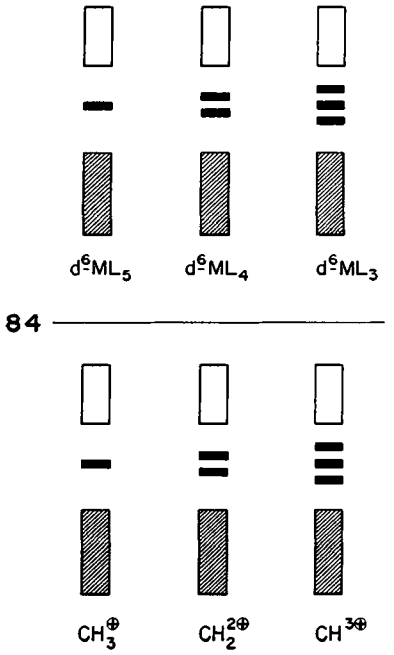
We next remove a ligand, a base, from the 18-electron complex. A localized hole on the metal, a directional hybrid, is created. The electron pair leaves with the ligand (cf. **83**). To put it in another way, in some localized description of the bonding, one M—L σ bond was formed by interaction of a ligand pair of electrons with a metal-based hybrid. Reversing the process, breaking the bond, frees that hybrid.



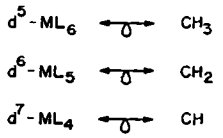
83

A parallel analysis for main group elements leads to the octet rule, since only s and p are considered as valence orbitals. Hybrids are freed by removing ligands, so that CH_3^+ has one vacant directional orbital, CH_2^{2+} has two such.

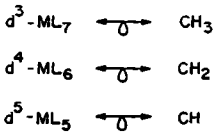
The parallel between ML_n and EL_n fragments (M = transition metal, E = main group element) is derived from the generation of similar hybrid patterns on removal of ligands from 18- or 8-electron configurations. For instance, if the octahedral polytype is used as a starting point, the 18-electron rule is satisfied for a d^6-ML_6. Then d^6-ML_5 will have one hybrid and no electrons in the gap between antibonding and bonding or nonbonding levels, just like CH_3^+, **84**: d^6-ML_4 will have two empty hybrids, so will CH_2^{2+}. The common form of the isolobal analogy follows from this.



The advantage of this alternative derivation is that it is easily extended to higher coordination numbers. For instance in any of the multitude of seven-coordinate geometries[8g] the 18-electron configuration is d^4. It follows immediately for fragments derived from these seven-coordinate structures that



From an eight-coordinate starting point[8p], where the 18-electron configuration is d^2:



The conclusions may be summarized in Table 1. Note once again the nonisomorphic, "many-to-one" nature of the isolobal analogy. Also, the results of the previous section on "Into the t_{2g} Shell" are contained in the present discussion.

Table 1. Isolobal Analogies.

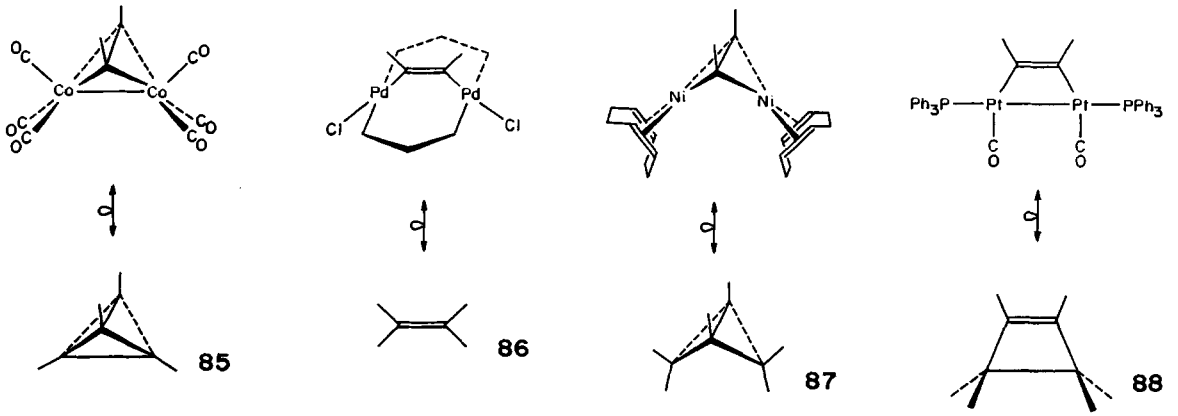
Organic Fragment	Transition Metal Coordination Number on which Analogy is Based				
	9	8	7	6	5
CH_3	d^1-ML_8	d^3-ML_7	d^5-ML_6	d^7-ML_5	d^9-ML_4
CH_2	d^2-ML_7	d^4-ML_6	d^6-ML_5	d^8-ML_4	d^{10}-ML_3
CH	d^3-ML_6	d^5-ML_5	d^7-ML_4	d^9-ML_3	

L = neutral two electron ligand.

Miscellanea

The general rules in hand, the cautions understood, one can proceed to apply the isolobal analogy. Indeed my strategy has been to show the applications as I introduced extensions of the model. Here are some additional examples:

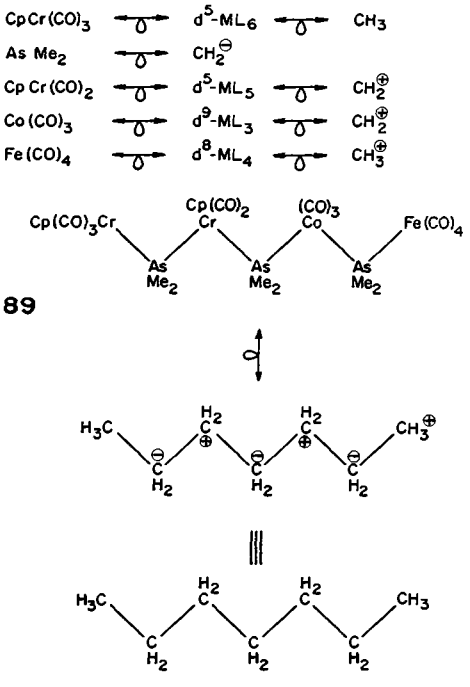
In a recent study of binuclear acetylene complexes the discussion focused on four structural types, **85**—**88**[41].



85 **86** **87** **88**

That these were isolobal with tetrahedrane, an olefin, bicyclobutane and cyclobutene was not only a curiosity, but actually made easier for us the complicated analysis of the interconversions of these molecules. And the isolobal analogy points to the synthesis of the as yet unknown "isomers" in the series, dimetallacyclobutadienes and butadienes, already known in complexed form.

Finally for amusement, consider the chain, **89**, assembled by *Vahrenkamp et al.*[42] (no implication is made in the simplified drawing of the chain stereochemistry.) There had better be a relationship to *n*-heptane! And so there is. We proceed using Table 1 as needed. $CpCr(CO)_3$ appears in a seven-coordinate guise here, so does $CpCr(CO)_2$; while $Co(CO)_3$ and $Fe(CO)_4$ are in a five-coordinate environment. It follows that:



89

Now it is simple—the inorganic chain **89** *is* really *n*-heptane!

One of Many Bridges

The isolobal analogy is a model. It is the duty of our scientific craft to push it to its extremes, and being only a model it is certain to fail somewhere, for any model, as ingenious a construction as it might be, is bound to abstract only a piece of reality. The reader has seen just how far the model can be pushed and where it breaks down.

The pleasing aspect of this particular model is that it brings together different subfields of our central science. We are separated, split asunder—organic, inorganic, physical, biological, analytical chemists—by the very largesse of our creation. The variety of molecules we create, and the methods we use to study them breed jargon and specialization. Yet underneath the seeming complexity there must be a deep unity. I think this approach would have pleased *R. B. W.*

It should be obvious to the reader that the spirit of this new line of work of my group owes much to what went on before. In particular I owe a direct debt of gratitude to my teachers M. P. Gouterman, W. N. Lipscomb, Jr., E. J. Corey, R. B. Woodward and my younger collaborators in the "organic days". E. L. Muetterties helped me learn inorganic chemistry. But it is my coworkers—graduate students, postdoctoral fellows, senior visitors—who in long group meetings, patiently yet with inspiration helped me shape this view of a piece of chemical experience. In rough chronological order of passing through Baker Lab in the "inorganic days" they are: M. Elian, N. Rösch, A. R. Rossi, J. M. Howell, M. M.-L. Chen, D. M. P. Mingos, A. B. Anderson, P. D. Mollère, P. J. Hay, J. C. Thibeault, P. Hofmann, J. W. Lauher, R. H. Summerville, T. A. Albright, D. L. Thorn, D. L. DuBois, Nguyen Trong Anh, A. Dedieu, E. M. Shustrovich, P. K. Mehrotra, M.-H. Whangbo, B. E. R. Schilling, K. Tatsumi, J. K. Burdett, H. Berke, A. R. Pinhas, S. Shaik, E. D. Jemmis, D. Cox, A. Stockis, R. D. Harcourt, R. D. Bach, O. Eisenstein, R. J. Goddard, H. H. Dunken, P. Kubáček, D. M. Hoffman, C. Mealli, Z. Havlas, C. N. Wilker, T. Hughbanks, S.-Y. Chu, S. Wijeyesekera, C. Minot, S. Cain, S. Sung, M. Kertész, C. Zheng. Kaz Tatsumi was especially helpful in the preparation of this paper.

I am in the business of communicating ideas to people. The graphical aspect of this enterprise, be it lecture slides or published articles, is critical. Throughout these years nearly

all of my drawings, containing countless "lined orbitals", have been expertly and beautifully executed by Jane S. Jorgensen and Elisabeth Fields, to whom I'm most grateful. The typing of my manuscripts and the associated details of production are the outcome of hard work by Eleanor R. Stolz and Eda J. Kronman, and I thank them for their help.

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Polarity of Binary Liquid Mixtures

By Heinz Langhals*

In contrast to the thoroughly studied polarity properties of pure liquids, only little is known about the polarity of mixtures of liquids, although the majority of mechanistic and preparative work is not carried out in pure phases. Using a widely applicable two-parameter equation, polar behavior of binary liquid mixtures can be described quantitatively as a function of their composition. Based on this equation, satisfactory explanations are found for deviations observed for binary solvent mixtures from the linear correlation of polarity scales, as well as for the unusual activation parameters estimated by *Winstein* for solvolysis of *tert*-butyl chloride. Applications of the equation range from a rapid test for determining water contents of solvents, the study of reaction mechanisms, to polymer chemistry.

1. Introduction

Solvent polarity has been interesting to chemists for some considerable time[1–4]. Macroscopic physical quantities, such as dielectric constant or refractive index are of only limited use for studying chemical reaction behavior and the associated molecular processes[1,5–8]: the development of the empirical polarity scales, however, was a substantial advance. The oldest, the *Y*-scale of *Winstein* and *Grunwald*[9–11], shown in equation (1), is based on the solvolysis of *tert*-butyl chloride and often correctly describes the influence of solvents on the rate of chemical reactions.

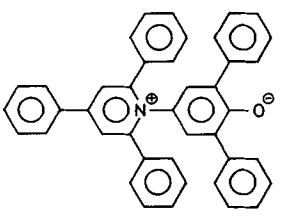
$$\lg \frac{k}{k_0} = Y \qquad (1)$$

k = rate constant of the solvolysis of $(CH_3)_3CCl$ in the medium to be studied

k_0 = rate constant of the solvolysis of $(CH_3)_3CCl$ in 80% ethanol-water.

2. Empirical Polarity Scales

Today, the Winstein *Y*-values are widely used as a primary polarity scale. Being derived from a solvolysis reaction, the *Y*-scale is, however, confined to polar media. Therefore, a number of other polarity scales[1] of wider applicability were developed, based on reaction kinetics or spectroscopic data. Scales derived from solvatochromism of dyes are noted for their straightforward and precise measurement[12,13]. Most remarkable is the $E_T(30)$-scale of *Dimroth* and *Reichardt*[14,15], which has become the most widely used scale: the solvatochromic dye pentaphenyl pyridiniumphenolate **1**, which serves as reference substance,



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exhibits a peak shift of its longest wavelength UV/VIS-absorption maximum—one of the largest known—when the solvent polarity is changed; moreover, it is soluble in almost all known solvents. The $E_T(30)$-values are the excitation energies [kcal·mol^{-1}] of **1** and are calculated from λ_{max} of the solvatochromic peak of **1** according to formula (2).

$$E_T(30) = 28\,590\ [\text{kcal}\cdot\text{nm}\cdot\text{mol}^{-1}]/\lambda_{max} \quad (2)$$

$E_T(30)$-values show good linear correlation with the *Y*-values of various solvents[1]. It is remarkable that such linear correlation of polarity scales is observed not only between $E_T(30)$ and *Y*, but also applies to most empirical scales[*].

The fact that a polarity concept applicable on the molecular scale exists, even if it is only comprehensible on an empirical basis, had important consequences for both mechanistic and preparative organic chemistry.

A few polarity scales do not correlate with the $E_T(30)$-scale (see Section 3.2). One, for example, is the donor number *DN* of *Gutmann*[16], which describes Lewis basicity rather than polarity of a solvent. The *DN*-scale has proved useful for describing processes involving the nucleophilicity of the solvent. It was recently attempted to include other such solvent properties together with polarity in a multi-parameter equation[17,18]. This evaluation corresponds to the principle of polylinearity (PPL) of *Palm*[19], and is similar to the multi-parameter evaluation of *Cramer*[20,21].

3. Binary Mixtures

For practical applications empirical polarity scales characterize polar behavior of liquids reasonably well. Surprisingly, however, the linear correlation which applies to pure solvents deteriorates when solvent mixtures are included[1,15,22]. However, such mixtures are rather useful for studying solvent effects, since the properties of various solvents can be adjusted continuously by changing the mixture ratio.

3.1. Polarity as a Function of Composition

A widely applicable equation containing only a few parameters for the quantitative description of the polarity of binary solvent mixtures as a function of their composition was long a key problem.

Dimroth and *Reichardt et al.*[14,15] used the $E_T(30)$-scale, for example, to study the polarity of the binary mixtures ethanol-water, isopropanol-water, methanol-water, acetone-water, 1,4-dioxane-water, pyridine-water, 2,6-lutidine-water, and piperidine-water as a function of their composition. Plotting the $E_T(30)$-values *versus* composition, expressed as vol.-% of one component, however, does not afford a linear relationship, as one might expect but strongly curved lines which could not, as previously found in other cases[1,20,23], be readily interpreted. Approximation of the complex functional curve has been attempted by Taylor series expansion[24] as well as by using several hyperbolic functions[25].

It was shown recently[26] that plotting $E_T(30)$-values against the logarithm of the molar concentration of the more polar component ($\ln c_p$) produces curves with a linear section. This is shown in Figure 1a for the typical mixture *N-tert*-butylformamide-benzene.

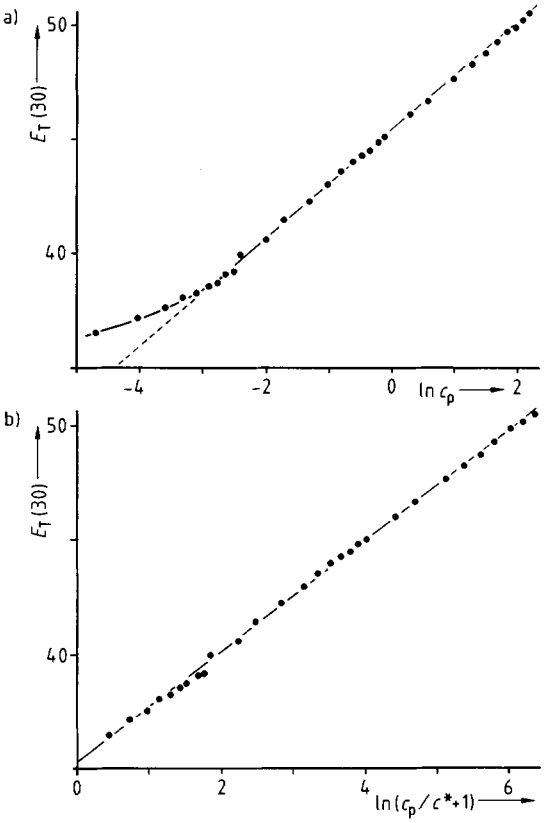


Fig. 1. $E_T(30)$-values for the mixture *N-tert*-butylformamide-benzene, a) as a function of $\ln c_p$, b) as a function of $\ln(c_p/c^* + 1)$ from equation (3).

In the study of solvolysis reactions, *Tommila*[27] also found curves with linear sections by plotting $\lg c_p$ of binary mixtures against the free activation enthalpy of solvolysis. The linear section was interpreted as arising from nucleophilic solvent participation in the reaction. Nucleophilic solvent participation of this type, however, is not possible in the case of the $E_T(30)$-scale.

Using the $E_T(30)$-scale with dye **1** as reference substance the course of the curve can be examined even at low concentrations c_p. In this region the curve deviates from linearity and as $c_p \rightarrow 0$ it tends to $E_T^0(30)$, the $E_T(30)$-value of the pure, less polar component (cf. Fig. 1a). Using the dual-parameter equation (3) the entire course of the curve can be described in closed form, including the curved section[26].

$$E_T(30) = E_D \cdot \ln\left(\frac{c_p}{c^*} + 1\right) + E_T^0(30) \quad (3)$$

$E_T(30)$ in equation (3) is the polarity of the binary mixture: $E_T^0(30)$ and c_p were explained above, and E_D and c^* are the parameters of the equation. They can be determined graphically[26,28] or using the POLAR computer program[26]. The validity of equation (3) can be demonstrated

[*] If a relationship between two scales is not only monotonic, but also linear, it can be concluded that both scales conform to the same law.

by plotting $E_T(30)$ against $\ln(c_p/c^* + 1)$ using, for example, the mixture *N-tert*-butylformamide-benzene (Fig. 1b). This produces a straight line which is shown covering a region of three orders of magnitude of c_p. Deviations from this linear section are statistical in nature and correspond to experimental error.

3.1.1. The Parameters of Equation (3)

The parameter E_D has the dimension of energy and is a measure of the sensitivity of the $E_T(30)$-scale towards relative changes of c_p. The parameter c^*, with the dimension of concentration, divides the curve in Figure 1a into two parts—this can be demonstrated by considering the limiting value of c_p[26]. If $c_p \ll c^*$, a linear relationship between $E_T(30)$ and c_p results, as can be shown by applying a series expansion to equation (3). Thus, in this concentration range, the contributions of both components to polarity are cumulative[*].

If, however, $c_p \gg c^*$ a linear relationship between $E_T(30)$ and $\ln c_p$ results. This case corresponds to the linear part of the curve in Figure 1a; thus, c^* divides this curve into a linear and a logarithmic part, and specifies the threshold value at which the two liquids start to interact according to equation (3).

The experimentally accessible range of c_p extends from the pure, less polar component, $c_p = 0$, to the pure, more polar component, $c_p = c_p^{max}$. As mentioned previously, the polar contributions of both components are approximately cumulative over the entire range, if $c^* \gg c_p^{max}$, and the frequently postulated linear relationship between polarity and composition of the mixture is satisfied (review: [1,2]). If, however, c^* is very small, say < 0.06 mol·L^{-1}, the correlation between polarity and c_p is non-linear over the experimentally relevant concentration range.

3.1.2. Further Polarity Scales

The conformity to a natural law indicated by equation (3) for the $E_T(30)$-scale has also been found with other polarity scales[29-31], and can be expressed in general form by equation (4).

$$P_G = E_D \cdot \ln\left(\frac{c_p}{c^*} + 1\right) + P_G^0 \qquad (4)$$

In equation (4) P_G is the polarity of the binary liquid mixture according to an empirical polarity scale and P_G^0 is the P_G value of the pure, less polar component. The parameters c_p, c^*, and E_D are as described in equation (3). Essentially, both equations show similar behavior when considering limiting values (see Section 3.1.1).

Empirical polarity scales, a selection of which is shown in Table 1, are based on various effects, such as $\pi \rightarrow \pi^*$ absorption (Nos. 1, 4–7), charge-transfer absorption (No. 3), fluorescence (Nos. 8, 9), and solvolysis (No. 2). The $E_T(1)$-scale (No. 5) responds not only to the polarity of the medium, but also shows sensitive response to its hydrogen bonding/donor character.

[*] Plotting $E_T(30)$ values against $\ln c_p$ produces a curved line: the left branch in Figure 1a.

In terms of the criteria used in all the polarity scales studied to date, equation (4) is a valid description of polar behavior of binary liquid mixtures as a function of their composition[29]. The linear relationship between P_G or $P_G - P_G^0$, respectively, and $\ln(c_p/c^* + 1)$, for some polarity scales mentioned in Table 1 is illustrated in Figure 2.

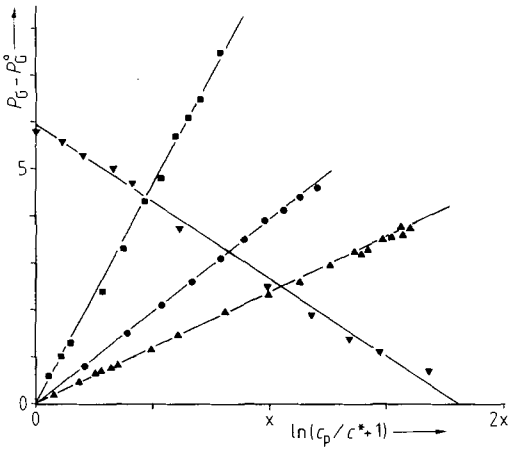


Fig. 2. Linear relationship between P_G and $\ln(c_p/c^* + 1)$ for various polarity scales (equation 4): ▲ $E_T(30)$ ethanol-1-decanol, x = 1; ● Y water-methanol, x = 1; ■ Z methanol-acetone, x = 2; ▼ π_1^* ethanol-*n*-heptane, x = 1, ordinate $P_G - P_G^0 + 5.8$.

Table 2 gives an impression of the range of validity of equation (4), and shows the results of applying it to the nine polarity scales in Table 1. The number and variety of the components used—polar protic, dipolar aprotic, and non-polar solvents, including aromatic solvents, were combined—lead to the conclusion that equation (4) provides a general description of the polarity of binary mixtures and is not confined to certain types of solvent[38]. Its validity for scale 5 and the mixture ethanol-water[29], which has a strong tendency to form H-bonds, is particularly notable. Thus, polarity effects caused by hydrogen bonding are also described by equation (4).

3.1.3. Special Cases

Special features are observed with the solvent mixture water-1,4-dioxane: up to a water content of *ca.* 50%, normal behavior according to equation (3) is observed with the $E_T(30)$-scale. At a certain critical concentration c_k, however, the linear relationship abruptly gives way to a second, steeper relationship with other E_D- and c^*-values[29].

In the following discussion, the concentration ranges $c_p < c_k$ and $c_p > c_k$ are designated region I and region II. For the mixture water-1,4-dioxane, the sudden change at c_k (discontinuity in the 1st derivative) can even be detected if $E_T(30)$ is plotted against $\ln c_p$, *i.e.* without introducing further parameters.

The existence of two regions of validity for equation (3) with a critical change at c_k could be interpreted by considering that largely isolated water molecules occur at low water concentrations in region I, and that formation of hydrogen bonded structures of water occur in region II. In another context it was postulated that 1,4-dioxane acts as a "solvent-structure-breaker"[39]. This model is consistent with the results of the polarity measurements.

Table 1. Empirical solvent polarity scales.

No.	Scala [a]	Reference Substance	Solvent dependent process	Definition [b]	Ref.
1	$E_T(30)$	**1**	$\pi\rightarrow\pi^*$-absorption	$E_T(30)=28590/\lambda_{max}$ [c]	[14, 15]
2	Y	**2**	Solvolysis relative to solvolysis in 80% ethanol/water (k_0)	$Y=\lg\frac{k}{k_0}$ [d]	[32]
3	Z	**3**	CT-absorption	$Z=28590/\lambda_{max}$ [c]	[12]
4	π_1^*	**4**	$\pi\rightarrow\pi^*$-absorption	$\pi_1^*=28590/\lambda_{max}$ [c, e]	[17, 18]
5	$E_T(1)$	**5**	$\pi\rightarrow\pi^*$-absorption	$E_T(1)=28950/\lambda_{max}$ [c]	[14]
6	*MOED*	**6**	$\pi\rightarrow\pi^*$-absorption	$MOED=28590/\lambda_{max}$ [c]	[13, 33, 34]
7	χ_R	**7**	$\pi\rightarrow\pi^*$-absorption	$\chi_R=28590/\lambda_{max}$ [c]	[13]
8	S_1	**8**, R = CH_3	fluorescence	$S_1=28590/\lambda_{max}$ [c]	[35–37]
9	S_2	**8**, R = H	fluorescence	$S_2=28590/\lambda_{max}$ [c]	[35]

[a] For other polarity scales, see [1]. [b] At 25 °C. [c] Molar excitation or emission energies in kcal·mol^{-1}; for conversion into SI units, multiply by the factor 4.2. [d] In Y units; for conversion into kcal·mol^{-1}, multiply by the factor 0.733. [e] In [17] molar excitation energies are stated in cm^{-1}. These were converted into kcal·mol^{-1} for direct comparison with other scales.

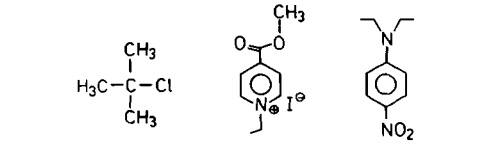
Table 2. The parameters E_D and c^* from equation (4) for binary solvent mixtures.

No.	Components [a]	c_P [b, c]	Reference substance	P_G^0 [d, e]	c^* [c, f]	E_D [d, f]	$\sigma(E_D)$ [g]	r [h]	n [i]	c_k [c, f]
1	1-Butanol–acetone	0.01–10.9	**1**	42.2	0.14	1.99	0.01	0.99952	31	—
2	Ethanol–acetone	0.02–17.1	**1**	42.2	0.14	2.27	0.02	0.99939	28	—
3	Methanol–acetone	0.03–24.7	**1**	42.2	0.10	2.53	0.02	0.99973	29	—
4	Wasser–acetone	0.06–55.4	**1**	42.2	0.31	2.83	0.02	0.99963	29	16.5 [k]
5	*N-tert*-Butylformamide–acetone	0.01–9.0	**1**	46.0	0.27	1.87	0.01	0.99948	31	—
6	Butanediol-1,4–acetonitrile	0.01–12.5	**1**	46.0	0.01	1.53	0.06	0.99749	31	—
7	Ethanol–acetonitrile	0.01–17.1	**1**	46.0	0.10	1.83	0.01	0.99972	30	12.0
8	1-Hexanol–acetonitrile	0.01–8.0	**1**	46.0	0.08	1.08	0.02	0.99876	29	—
9	Methanol–acetonitrile	0.03–24.7	**1**	46.0	0.06	1.83	0.03	0.99877	31	—
10	Water–acetonitrile	0.06–49.8	**1**	46.0	0.15	2.07	0.02	0.99877	27	—
11	*N-tert*-Butylformamide–benzene	0.01–9.0	**1**	35.2	0.017	2.42	0.02	0.99935	30	—
12	Water–*tert*-butyl alcohol	0.06–33.2	**1**	43.9	1.01	2.82	0.05	0.99666	26	—
13	Water–*tert*-butyl hydroperoxide	0.4–7.4	**1**	49.7	0.312	1.40	0.02	0.99922	12	—
14	Ethanol-1-decanol	0.02–17.1	**1**	47.6	4.09	2.35	0.02	0.99915	30	—
15	1-Butanol–dimethylformamide	0.01–10.9	**1**	43.8	1.64	3.20	0.02	0.99936	30	8.7
16	Ethanol–dimethylformamide	0.02–17.1	**1**	43.8	0.607	2.78	0.04	0.99792	30	13.7
17	Methanol–dimethylformamide	0.03–24.7	**1**	43.8	0.696	3.55	0.05	0.99745	31	—
18	Water–dimethylformamide	0.06–38.8	**1**	43.8	11.43	9.24	0.18	0.99527	27	—
19	1-Butanol–dimethyl sulfoxide	0.01–10.9	**1**	45.0	4.29	4.93	0.1	0.99475	30	7.7
20	Ethanol–dimethyl sulfoxide	0.02–17.1	**1**	45.0	2.69	3.95	0.05	0.99794	30	13.7
21	Acetonitrile-1,4-dioxane	0.02–19.1	**1**	36.0	0.77	3.23	0.03	0.99909	29	—
22	1-Butanol-1,4-dioxane	0.01–10.1	**1**	36.0	0.90	5.39	0.03	0.99973	30	—
23	Ethanol-1,4-dioxane	0.02–17.1	**1**	36.0	0.72	4.99	0.03	0.99975	30	—
24	Methanol-1,4-dioxane	0.03–3.0	**1**	36.0	0.98	7.67	0.03	0.99980	20	3.0
25	Methanol-1,4-dioxane	3.0–24.7	**1**	(32.) [m]	0.089	4.09	0.08	0.99828	10	(3.0)
26	Nitromethane-1,4-dioxane	0.02–18.6	**1**	36.0	1.01	3.49	0.03	0.99929	31	—
27	Propiononitrile-1,4-dioxane	0.01–14.1	**1**	36.0	1.41	3.33	0.03	0.99834	30	—
28	Water-1,4-dioxane	0.6–55.4	**1**	36.0	0.58	4.34	0.05	0.99922	22	22.0 [f]
29	Water–ethanol	0.06–55.4	**1**	51.9	6.83	1.64	0.04	0.99232	27	—
30	1-Butanol–nitromethane	0.01–10.9	**1**	46.3	0.06	1.43	0.02	0.99914	31	6.5
31	Ethanol–nitromethane	0.02–17.1	**1**	46.3	0.03	1.41	0.03	0.99704	30	8.5
32	Methanol–nitromethane	0.03–22.2	**1**	46.3	0.01	1.66	0.02	0.99947	29	10.0
33	Water-1-propanol	0.06–55.4	**1**	50.7	4.34	1.70	0.02	0.99768	30	36
34	Acetone–pyridine	0.03–12.2	**1**	40.2	32.06	4.01	0.13	0.98710	28	—
35	1-Dodecanol–pyridine	0.004–4.5	**1**	40.2	0.89	2.90	0.03	0.99901	30	3.0
36	Ethanol–pyridine	0.02–17.1	**1**	40.2	12.75	9.64	0.17	0.99554	31	-
37	1-Hexanol–pyridine	0.01–8.0	**1**	40.2	1.11	2.90	0.05	0.99763	30	-
38	Methanol–pyridine	0.03–24.7	**1**	40.2	5.84	6.92	0.08	0.99802	31	-
39	Nitromethan–pydridine	0.02–18.6	**1**	40.2	13.62	6.46	0.14	0.99384	30	-
40	*tert*-Pentanol–pyridine	0.005–8.3	**1**	40.2	0.95	1.02	0.03	0.99341	29	-
41	Water–pyridine	0.06–49.8	**1**	40.2	5.48	7.09	0.12	0.99599	29	-
42	1-Butanol–CS_2	0.01–10.9	**1**	32.6	0.03	2.42	0.03	0.99906	30	7.5
43	1-Octanol–CS_2	0.01–6.4	**1**	32.6	0.06	2.83	0.06	0.99676	30	4.0
44	Pinacolone–CS_2	0.3–8.0	**1**	32.6	7.89	9.30	0.26	0.99459	16	—
45	1-Butanol–tetramethyl urea	0.01–10.9	**1**	41.0	0.91	3.56	0.03	0.99936	31	—
46	Ethanol–tetramethyl urea	0.02–17.1	**1**	41.0	0.81	3.51	0.03	0.99925	31	—
47	Water–ethanol	0.06–30	**2**	−2.05	7.48	0.64	0.01	0.99956	12	25
48	Water–methanol	0.06–55.4	**2**	−1.12	24.0	3.91	0.03	0.99972	11	—
49	Methanol–acetone	0.03–24.7	**3**	66.3	0.65	4.66	0.01	0.99993	31	—
50	Ethanol–acetonitrile	0.02–17.1	**3**	72.2	0.80	2.76	0.04	0.99781	47	6.8
51	Methanol–1,4-dioxane	0.03–24.7	**3**	63.0	2.66	8.52	0.18	0.99384	31	—
52	Water–ethanol	0.06–55.4	**4**	74.8	3.08	−1.71	0.02	−0.99846	31	25
53	Ethanol–*n*-heptane	0.02–17.1	**4**	78.7	2.93	−3.13	0.04	−0.99681	33	—

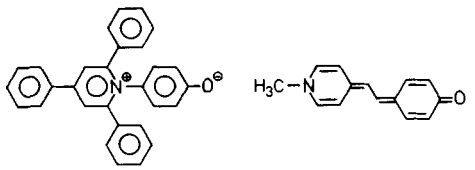
Table 2. Continuation

No.	Components [a]	c_p [b, c]	Reference substance	P_G^0 [d, e]	c^* [c, f]	E_D [d, f]	$\sigma(E_D)$ [g]	r [h]	n [i]	c_k [c, f]
54	Water-ethanol	0.06–55.4	**5**	35.2	49.7	6.67	0.10	0.99740	34	25
55	Methanol-acetone	0.03–24.7	**6**	49.3	0.31	2.25	0.01	0.99952	30	—
56	Water-ethanol	0.06–55.4	**6**	55.9	5.47	2.04	0.06	0.99186	24	25
57	1-Butanol-nitromethane	0.01–10.9	**7**	44.4	2.86	−1.15	0.15	−0.98776	31	4.4
58	Methanol-acetone	0.03–4.0	**8**	61.2	0.50	−2.19	0.02	−0.99962	22	4.0
59	Methanol-acetone	4.0–25	**8**	(58.3) [m]	2.11	−1.58	0.01	−0.99983	10	(4.0)
60	Wasser-1-propanol	0.06–55.4	**8**	54.7	1.53	−0.47	0.01	−0.99604	31	36

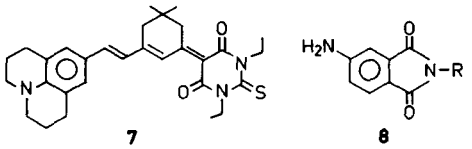
[a] The more polar solvent is mentioned first; both components in alphabetical order. [b] Concentration range studied. [c] In mol·L^{-1}. [d] In kcal·mol^{-1}. [e] P_G value of the less polar component, see [2]. [f] See text. [g] Variance of E_D. [h] Correlation coefficient of equation (4). [i] Number of points. [k] If $c_p > c_k$, $E_D = 6.8$ and $c^* = 6.1$. [l] If $c_p < c_k$, $E_D = 20.0$ and $c^* = 19.1$. [m] Extrapolated value.



2 **3** **4**



5 **6**



7 **8**

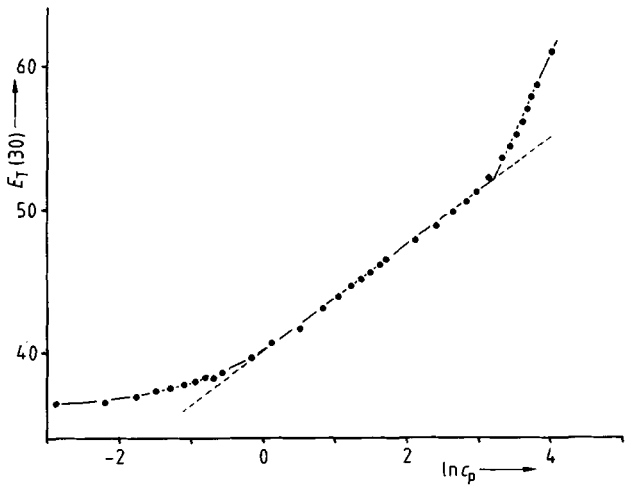


Fig. 3. Double line for the mixture water-1,4-dioxane (No. 28).

In Figure 3, the linear part of region I can be extrapolated into region II (broken line; an even more exact result is achieved by plotting against $\ln(c_p/c^* + 1)$ instead of $\ln c_p$). Thus, for $c_p = c_p^{max}$, a virtual polarity value is obtained for water, $P_V = 56$, which is smaller than the actual polarity value of 63.1[2]. P_V is the polarity with which water, as the more polar component, affects dioxane within region I. Since the effective polarity of water is substantially lower at high dilution than in concentrated solutions, one might venture to conclude that specific interaction of water molecules in molecular associates is responsible for the high polarity of pure water, rather than the characteristics of the isolated water molecule.

The occurrence of a second, steeper line according to equation (3) is not confined to the mixture water-1,4-dioxane, but can also be observed with other mixtures, especially with those including water, *e.g.* water-acetone[40]. The mixture water-ethanol has been studied extensively using several polarity scales[29]. All the scales studied produced double lines (three examples are shown in Figure 4).

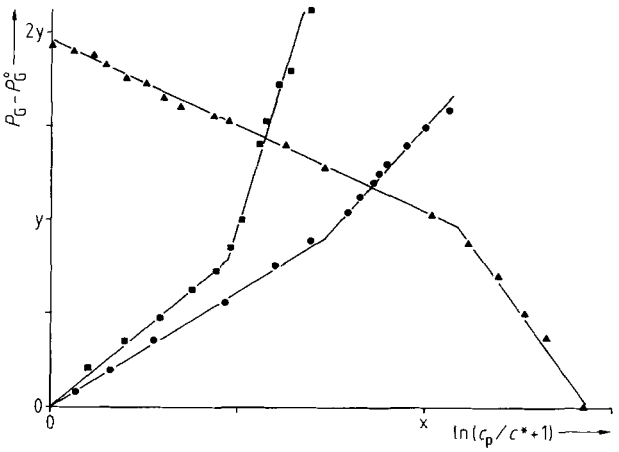


Fig. 4. Double lines according to equation (4) for the mixture water-ethanol (No. 29): ● Y, x = 2, y = 1; ■ $E_T(1)$, x = 1, y = 4; ▲ π_1^*, x = 1, y = 4, ordinate: $P_G - P_G^0 + 7.7$.

It is remarkable that the various polarity scales produce c_k-values which coincide within the limits of experimental error[*]. Thus, the double-line phenomenon is not peculiar to the $E_T(30)$-scale, but must be taken as a characteristic of the binary mixture water-ethanol. This problem will be discussed in more detail in Section 4.1.

Even more interesting than the examples mentioned above are mixtures of 1-butanol and acetonitrile or nitromethane, and of ethanol and nitromethane, which repre-

[*] In Figure 4 the break points appear at different abscissae since the c^* values vary for each polarity scale.

sent a further type of binary mixture[31]. Here, also, two straight lines are observed. The second line, however, has a negative slope, contrary to the previous cases. This is shown in Figure 5 for the mixture 1-butanol-nitromethane.

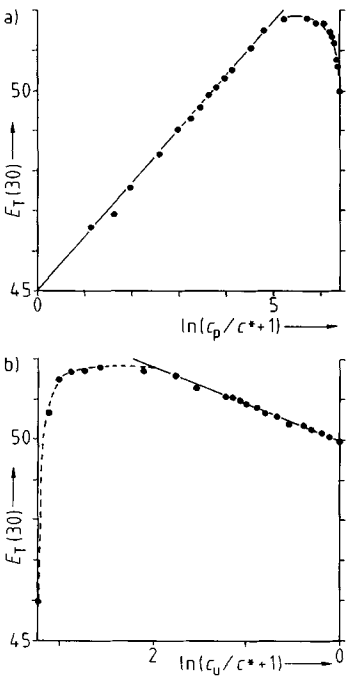


Fig. 5. Relationship between $E_T(30)$ and a) $\ln(c_p/c^*+1)$ and b) $\ln(c_u/c^*+1)$ for the mixture 1-butanol-nitromethane.

The polarity of the mixture increases as c_p increases and reaches its maximum at c_k. As c_p increases further, however, the polarity again decreases and attains the polarity value of the pure, more polar component at c_p^{max}. Within region I, $c_p < c_k$, normal behavior according to equation (3) is observed (see Fig. 5a). Within region II, however, nitromethane, which as a pure substance is less polar, interacts with 1-butanol like a more polar additive. Accordingly, in this region there is a linear relationship between $E_T(30)$ and $\ln(c_u/c^*+1)$, where c_u is the molar concentration of the less polar component (Fig. 5b). By analogy to the previous examples, a virtual polarity can be defined for the polar component 1-butanol. Contrary to these previous cases, however, it is greater than the actual polarity of the alcohol.

Mixtures with $c_p = c_k$ are substantially more polar than their components. This phenomenon, known as "elevated polarity"[31] or the "synergetic polarity effect"[41], can be explained by a hydrogen-bond/donor-acceptor model: the additive, which itself has low polarity, promotes the formation of a polar solvent structure. This behavior is remarkable insofar as it contradicts the usual view that the polarity of a solvent mixture lies within the limits of the polarity of its components; furthermore, the polarity of solvents can be enhanced by adding less polar components.

3.2. Slow and Fast Processes

The majority of polarity scales show mutual linear correlation and with the *Y*- and $E_T(30)$-scales, as far as pure solvents are concerned. A few scales form an exception, but these also mutually correlate. This behavior typically occurs with weakly polar merocyanines with positive solvatochromism[6,42]. One of the first cases to be studied is *Brooker*'s[13] χ_R-scale (Table 1, No. 7), which is based on the solvatochromism of dye **7**. Polarity scales such as χ_R will be discussed extensively here, particularly their application to binary solvent mixtures.

Studies of the solvatochromism of phthalimide derivatives **8** indicate that these exhibit strongly positive solvatochromism in fluorescence phenomena, and this was proposed as the basis for the *S* polarity scale by *Zelinski et al.*[35,36] (for the influence of oxygen, cf. [37]). Absorption by these dyes is also solvatochromic[30]. A linear relationship with the $E_T(30)$-scale exists for fluorescence, but for absorption a linear relationship with the χ_R-scale is observed. Thus, dye **8** is especially suitable for clarifying the previously mentioned exceptions, since it supplies a common basis for both groups of polarity scales.

It is known that the ground state (S_0) of **8** has only a small dipole moment; however, the first electronically excited state (S_1), has a large dipole moment[7]. The different behavior of **8** in absorption and emission can be explained by assuming that states with large dipole moments are strongly solvated by polar solvents, whereas states with small dipole moments are solvated weakly: the Franck-Condon principle for electronic transitions applies to the solvating shell of a dye[43]. The electronic transition takes place in such a short period of time that solvation is unable to follow by reorienting the solvent molecules. Consequently, orientation will only influence solvation in the initial state of an electronic transition, but not the final state. The latter will still bear the solvating shell of the initial state, and can only be stabilized by polarization effects. Absorption and fluorescence of **8** proceed as given in the scheme in Figure 6. The initial state, S_0, is little influenced by polar solvents.

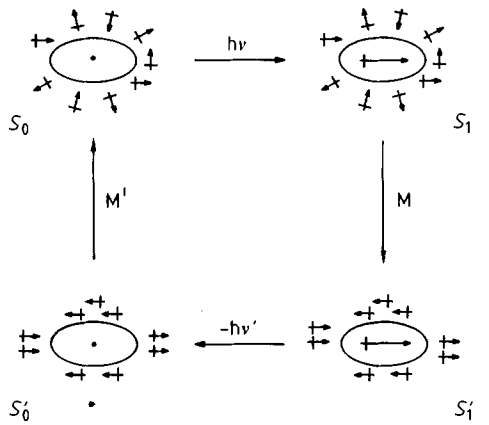


Fig. 6. Schematic representation of absorption and emission processes of dye **8** in polar solvents.

The excited state, S_1, has a large dipole moment, but is surrounded by the solvating shell of the S_0 state. Thus, solvent polarization effects are crucial for absorption—by analogy to the χ_R scale.

Excitation is followed by relaxation of the solvating shell; the lifetime of the excited state (S_1) of *ca.* 10^{-8} to

10^{-9} s is long enough to permit a more favorable orientation of the solvent molecules surrounding the dye molecule. The transition from S_1 to S_1' corresponds to the modification (M) as described for reactions of the excited state in which the excitation energy is conserved[44]. Finally, the transition from S_1' to S_0' occurs by fluorescence, the energy of which is fully influenced by solvent orientation phenomena (besides polarization effects) because the dipole moment of the initial state of this electronic transition is large. It is therefore reasonable that the fluorescence of **8** correlates with the $E_T(30)$-scale. The absorption of dye **1** is subject to an analogous situation. However, in most cases, the behavior of other dyes is by no means as extreme as the absorption of **7** or **8**, and a combination of polarization and orientation effects are observed. Frequently, however, the orientation phenomena prevail, and this results in correlation with the $E_T(30)$-scale. These considerations allow the conclusion to be made that dye **7** (χ_R scale) is a polarity indicator for short measuring times, whereas dye **1** ($E_T(30)$ scale) is suitable for long measuring times (cf. the concept proposed by *Bakhshiev*[45]). In organic chemistry the orientation of the solvent, a relatively slow process, is of crucial influence. Thus, it is reasonable that such processes are correctly described by the $E_T(30)$-scale.

Equation (4) characterizes the polar behavior of binary liquid mixtures according to the χ_R-scale or to an absorption scale using dye **8** as reference. Thus, it can be concluded, that equation (4) will also describe the polar behavior of binary solvent mixtures in fast processes. Equation (4) cannot, therefore, be solely attributed to the concentration of the polar solvent on the surface of the dye[46,47]. Further information on solvent structure is provided by comparing the c^* values of dye **8** in solvent mixtures for absorption and emission[30].

4. Applications of Equation (4)

Equation (4) characterizes, quantitatively, the polar behavior of binary liquid mixtures, and there are no shortage of examples of its use as a "tool" in many areas of chemistry. Applications to mechanistic problems are discussed first.

4.1. Solvolysis of *tert*-Butyl Chloride in Ethanol-Water

The discovery of the Winstein relationship[9], which is based on the solvolysis of *tert*-butyl chloride, played a key role in the development of the empirical polarity concept. Subsequently, *Winstein* studied the influence of temperature on the solvolysis of *tert*-butyl chloride in ethanol-water mixtures[11]. The free energy of activation, $\Delta G^{\neq}$, of this reaction decreases as a monotonic function without strong curves as the water content of the mixture is decreased: the course of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, however, is more complex and maxima and minima occur (see Fig. 7).

This unusual and surprising behavior led to numerous speculations[6,39,48-54]. A satisfying explanation of the experimental data published 25 years ago has yet to be found. It seems to contradict experience that the $\Delta G^{\neq}$ value, which is composed of enthalpy and entropy terms has a

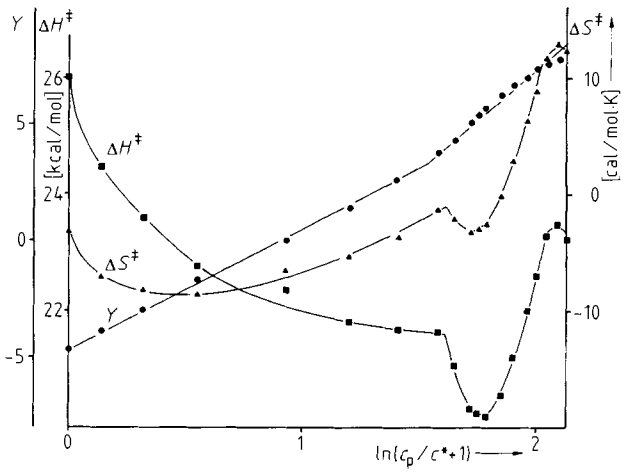


Fig. 7. Thermodynamic data for the solvolysis of *tert*-butyl chloride in ethanol-water [11].

simple functional course, and that the apparently simpler quantities $\Delta H^{\neq}$ and $\Delta S^{\neq}$, however, appear so complicated. Since the solvolysis of *tert*-butyl chloride is sensitive to polarity changes in the medium, an analysis of *Winstein*'s and *Fainberg*'s measurements using equation (4) appears appropriate. As shown in Figure 8, the free energy of activation $\Delta G^{\neq}_{298}$ of the solvolysis of *tert*-butyl chloride in ethanol-water mixtures and the correspondingly proportional quantities $\ln k_{298}$ or Y can be described quantitatively by equation (4) as a function of composition.

An interesting point is—as with other polarity scales (see Section 3.1.3)—that two regions of validity of equation (4) with a critical transition point at $c_k \approx 25$ mol·L^{-1} (double lines) are observed. Thus, the free entropy of activation shows nothing anomalous. The high precision of *Winstein*'s kinetic measurements must be stressed; this is clearly expressed by the lines in Figure 8 and Figure 2.

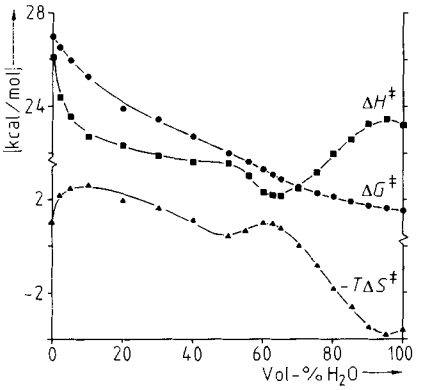


Fig. 8. Analysis of solvolysis data of *tert*-butyl chloride in ethanol-water according to equation (4).

The activation enthalpy $\Delta H^{\neq}$ and the activation entropy $\Delta S^{\neq}$ of the reaction were calculated from the rate constants at only two temperatures, respectively[11], in the range 0 to 45 vol.% water at 25° and 50 °C and in the range of 50 to 100 vol.% water at 0° and 25 °C. It can be shown that for the series of measurements at 0 °C and 50 °C equation (4) also holds (see Table 3); their E_D and c^* values are only slightly different from the measurements at 25 °C.

Table 3. Application of equation (4) to the Winstein scale.

T [a]	Range [b]	E_D [c]	c^* [d]	Y^0 [e]	r [f]	n [g]
25	I	2.9	11.6	− 1.97	0.9991	9
50	I	2.4	9.7	− 0.52	0.9998	7
0	II	2.6	0.001	(−26.9)	0.9845	12
25	II	2.7	0.001	(−26.1)	0.9935	10
(ΔH^+) [b]	I	−0.944 [i]	0.26	(26.1) [h, i]	0.9996	6

[a] Temperature in °C. [b] See text. [c] In Y units. [d] mol·L^{-1}. [e] Extrapolated Y value for ethanol. [f] Correlation coefficient. [g] Number of points. [h] Activation energy. [i] In kcal·mol^{-1}.

The change of temperature from 0° to 50 °C for the calculation of the activation data was conducted at a water concentration of *ca.* 25 mol·L^{-1} (the second temperature was 25 °C in all cases). By chance, this value coincides approximately with the value of c_k corresponding to the intersection point of the two lines in Figure 8. Based on this, the course of the functional curve of ΔH^+ in Figure 7 can be characterized.

For $c_p < c_k$ (region I, $\Delta H^+ \sim \ln k_{298} - \ln k_{323}$), ΔH^+ is a monotonic function of the water content. The E_D and c^* values of $\ln k$ are only slightly different at 25 and 50 °C. Thus, even the solvent dependence of ΔH^+ is approximately described by equation (4) (Table 3). In this correlation the expansion of the liquid must be taken into account, since at a given content in vol.% the molar water content is temperature dependent.

In the region $c_p \approx c_k$ a number of factors cause ΔH^+ to have a rather complex dependence on concentration. Going beyond c_k, its temperature dependence and the temperature change have the effect that the individual measurements for determining ΔH^+ are made partly in region I and in region II. This results in the unusual functional course of ΔH^+.

Finally, in the region $c_p > c_k$ (region II) a monotonic dependence of the ΔH^+ values on the solvent composition is observed, as in region I. The additional maximum at very high water contents may be a result of mixing problems and will not be discussed here (this is dealt with in [48, 55]). The concentration dependence of ΔS^+ (Figs. 7 and 8), can be explained in an analogous manner to the difference between ΔH^+ and ΔG^+.

The solvolysis of *tert*-butyl chloride in ethanol-water, discussed here at length, is characteristic of other solvolysis reactions in solvent mixtures[39, 52, 53, 56, 57], which can be treated in an analogous way, and is also generally typical of mechanistic studies in them. Furthermore, the reference point of the Y-scale, 80 vol.% ethanol/water, may present problems if the temperature differs substantially from 25 °C.

Another result of the previous analysis is of general interest: for reactions influenced by the polarity of the medium, the free energy of activation, ΔG^+, should, at least in solvent mixtures, be a more simple parameter than ΔH^+ and ΔS^+, since these always contain contributions from the thermal expansion of the liquid, which are not reaction-specific. Special attention is, therefore, required when a solvent mixture exhibits two regions of validity of equation (4) (cf. also Section 4.2).

4.2. Nonlinear Winstein Relationships

The results just mentioned lead to other applications of equation (4) to mechanistic studies: Linear correlation of a process with the Winstein relationship is often used as a mechanistic criterion, by analogy to other linear free energy (LFE) relationships (*e.g.* see [32, 60–64]). In the first place, the value m, the slope of the straight line, is interpreted as a measure of the sensitivity of the reaction studied to solvent polarity effects, and is often related to increase or decrease of charge separation leading to the transition state. Furthermore, a linear correlation over a large range of solvent polarity is used as an indication of a uniform reaction mechanism in different solvents. In order to obtain a sufficient number of measurements, reactions are usually studied using solvent mixtures, often ethanol-water.

As the polarity of these mixtures is governed by equation (4), it seems worthwhile to redefine the previously mentioned mechanistic criteria on the basis of equation (4).

From equation (4), the slope m of a relationship between two polarity-dependent processes P_{G1} and P_{G2} is described by equation (5).

$$m = \frac{dP_{G1}}{dP_{G2}} = \frac{E_{D1}(c_p + c_2^*)}{E_{D2}(c_p + c_1^*)} \tag{5}$$

A good linear relationship between P_{G1} and P_{G2} requires that the slope m in equation (5) is independent of c_p, and hence, one of the following three conditions must be fulfilled:

1. The c^*-values of both processes are similar ($c_1^* \approx c_2^*$). The logarithmic term in equation (4) has an approximately equal numerical value in both cases for a given value of c_p. Consequently, P_{G1} and P_{G2} are linearly dependent.
2. The c^*-values are different in both cases, but considerably larger than c_p^{max} ($c_1^*, c_2^* \gg c_p^{max}$). Equation (4) can be expanded in both cases as a Taylor series, which as usual is terminated. A linear relationship between P_G and c_p results and, likewise, a linear relationship between P_{G1} and P_{G2}.
3. The c^*-values are different, but both very small. In each case P_G and $\ln c_p$ are linearly dependent and, therefore, also P_{G1} and P_{G2}.

Often, one of these three conditions is fulfilled. However, if a nonlinear relationship is found, *e.g.* with the Winstein scale, it does not necessarily follow that there is a change in mechanism, or even that a continuous transition from one mechanism to another occurs upon varying the medium (cf. also [65]). This information is obtained only by estimating the c^*-values.

Even more complicated is the influence of the solvent and its dependence on c_p when mixtures with critical transition points (double lines) are used. These are observed particularly when solvolysis reactions are carried out in frequently-used binary mixtures such as acetone-water, 1,4-dioxane-water and ethanol-water (see Table 2)[29, 40]. An example for the mixture ethanol-water is described here.

Brown et al.[66] studied the solvolysis of isopropyl, cyclohexyl, and 2-adamantyl tosylates in ethanol-water. The free energies of activation show good linear correlation with the *Y*-scale up to a water content of *ca.* 50%. At higher water contents, substantial deviations are observed, which represent a regular break in the LFE relationship (Fig. 1 in [66]). Nucleophilic solvent participation with a change in reaction mechanism was discussed. This appears to be contradicted by the behavior of isopropyl tosylate, which, although hardly shielded and easily accessible to nucleophilic attack, shows the smallest deviations. These were finally attributed to a specific solvation of the leaving anion, since the corresponding mesylates show linear relationships with the *Y*-scale.

The solvolysis data can be analyzed on the basis of equation (4). The break in the LFE relationship is observed at a water content of *ca.* 50% and can be interpreted as a critical transition point (see Section 3.1.3). Since similar c^* values are found for the solvolysis of *tert*-butyl chloride and the various tosylates, a discussion of the E_D values according to equation (5) is sufficient. For *tert*-butyl chloride and cyclohexyl mesylate (Table 4, Nos. 1 and 2), the ratio of the E_D values is almost equal in regions I and II. Thus, an approximate LFE relationship is observed for the entire water concentration range. The relatively low E_{DII} value of No. 2 even explains the slight deviations at high water contents.

Table 4. Solvolyses [11, 66] in solvent mixture ethanol-water at 25 °C.

No.	Substrate	Region I			Region II		
		E_{DI} [a]	c_I^* [b]	$\ln k_{0I}$ [c]	E_{DII} [a]	c_{II}^* [b]	$\ln k_{0II}$ [c]
1	*tert*-Butyl chloride	6.7	11.6	−16.1	6.3	0.001	− 7.16
2	Cyclohexyl mesylate	4.7	10.8	−17.3	4.6	(0.001) [d]	—
3	2-Adamantyl tosylate	4.7	8.3	−21.6	9.9	0.001	−11.7
4	2-Propyl tosylate	3.2	12.9	−14.7	5.0	(0.001) [d]	—
5	Cyclohexyl tosylate	8.3	32.8	−16.8	7.7	0.001	− 9.1

[a] In $\ln k_{298}$ units. [b] In mol·L^{-1}. [c] Value for pure alcohol extrapolated from equation (4). [d] Estimated, since too few points available for calculation.

The tosylates, however, behave quite differently (Table 4, Nos. 1, 3, and 4). The much higher values of E_D in region II result in LFE relationships, whose slopes are almost twice as large as those in region I. Therefore, breaks in the relationships must exist at c_k (Fig. 1 in [66]). The c^* value of cyclohexyl tosylate (Fig. 4, Nos. 1 and 5) no longer coincides well with that of No. 1. Appropriately, the resulting LFE relationship is considerably inferior. In this case, a simple comparison of the E_D values is not sufficient. Detailed analysis, however, shows that No. 5 behaves in the same way as Nos. 3 and 4. The solvolysis reactions in acetone-water mixtures can be analyzed in an exactly analogous manner.

Sridharan and *Vitullo*[64] studied the solvolysis of geminal dihalides in 1,4-dioxane-water. Here, also, the LFE relationship with the *Y* scale turned out to be nonlinear, with two straight lines. This was attributed to a change of reaction mechanism and transition to nucleophilic solvent participation. It can be shown, however, that the critical transition point of the 1,4-dioxane-water mixture coincides with the point of intersection of the two lines.

The last examples show that the existence of an LFE relationship is a limited mechanistic criterion for studying solvent-dependent processes in solvent mixtures. Therefore, when examining such processes, binary mixtures should be checked for critical transition points.

4.3. Further Applications

Using equation (4) conclusions about the composition of binary liquid mixtures can be made by considering polarity-dependent phenomena[28,40,67]. Mixtures can be analyzed in this way. Suitable reference substances are solvatochromic dyes. The water content of organic solvents can be estimated by this method, since water has a greater polarity than most organic liquids. The use of solvatochromic dyes in practice was hitherto hampered by the nonlinearity of the calibration curve, which necessitated a great number of experimental points at low water concentrations[68]. Using equation (4) it is now possible to linearize these calibration curves, so that only a few points are necessary. Apart from this, the quasi-logarithmic relationship of equation (4) furnishes the advantage of an almost constant relative error in measurement over a wide concentration range[40]. For a rough estimation of water concentration, even visual comparison with a color scale is sufficient. Solvents such as dimethylformamide or dimethyl sulfoxide present no problems, in contrast to what is experienced with other methods. Colored solutions can be examined in an analogous manner using solvatochromic fluorescent dyes. A triple point method of measurement even dispenses with a fluorescence spectrometer[67].

Furthermore, the polarity of a solution can be adjusted accurately by means of equation (4). This is of interest, when a compound reacts by different mechanisms in polar and nonpolar media. An example is the thermolysis of percarboxylic esters[69] which in nonpolar media generally proceeds homolytically with radical formation; in polar media, however, heterolysis occurs according to the Criegee mechanism. If generation of radicals in a polar medium is desired, it is advantageous to adjust the polarity of the medium to a point at which homolysis just prevails.

In other cases, where the addition of a small amount of polar additive should enhance the solvent polarity as much as possible[44], c^* plays a key role. If $c_p < c^*$, the polarity is strongly dependent on c_p, but if $c_p > c^*$, only to a small extent (this relationship is roughly logarithmic). In order to markedly enhance the polarity by addition of only a small amount of polar additive, c_p should be adjusted to approximately c^*.

Furthermore, it can be concluded from equation (4) that addition of a small amount of polar additive to a solvent of low polarity can enhance the polarity substantially; on the other hand, introducing a nonpolar additive to a polar medium produces hardly any reduction of polarity. This observation corresponds to a considerable amount of empirical data, for example, in chromatography, where polar additives have far greater influence on elution behavior than nonpolar. Polymer chemistry is another field of application for equation (4), where it is not only valid for liquids, but even holds for solids[70]: on the one hand, it character-

izes the effect of polar components on copolymerizations and on the other, that of low-molecular weight additives (plasticizers). This is useful in devising procedures for manufacturing polymers with specific properties.

5. Outlook

Apart from the previously described areas of chemistry, equation (4) can be utilized in many others which can only be mentioned briefly here. In the study of reaction mechanisms, an opportunity is provided to characterize the influence of the medium on a chemical reaction, even when the polarity varies as the reaction progresses. Since equation (4) even describes the polarity of pure alcohols as a function of their chain length[71], it can be expected that the polarity of the pure substances can be composed of increments. The correlations are, however, nonlinear.

Polymer chemistry, offers yet another field of application. Not only can equation (4) be of use in adjusting the polarity of the polymer to a particular value, in the methodical determination of polar additives which enhance polarity even at low concentrations, and in obtaining information on the effect of residual monomer[70], but it also offers the possibility of obtaining information on copolymerization parameters and on interactions between polymers. Finally, preliminary studies on ternary liquid mixtures show that equation (4) can be extended to multi-component systems.

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Oxygen Transfer from Inorganic and Organic Peroxides to Organic Substrates: A Common Mechanism?

By Hubert Mimoun*

In this progress report an attempt is made to rationalize, from a mechanistic point of view, the different ways in which oxygen is transferred from inorganic and organic peroxides to nucleophilic substrates, particularly olefins. Oxygen transfer from transition-metal peroxides, which is relevant to catalytic oxidations using O_2, H_2O_2 or ROOH, occurs *via* a cyclic or "pseudocyclic" peroxymetalation in which a dioxametallacycle is formed. Owing to the wide discrepancy between peroxymetalation and the conventional oxidation mechanism, *i.e.* nucleophilic attack of the substrate at the electrophilic "active oxygen", we propose an alternative mechanism involving dioxiranes as the reactive species. The generation of dioxiranes appears to be a common denominator in the reactions of most organic peroxides *e.g.* peroxy acids, the reaction of electrophilic ketones with H_2O_2, or ozonizations. Oxygen transfer from dioxirane reagents probably involves the formation of a charge-transfer π-complex between the substrate and the carbon atom of the dioxirane, and the subsequent formation of a cyclic peroxidic intermediate.

1. Introduction

Molecular oxygen, one of the most abundant elements on earth, has until now scarcely been used for the selective oxidation of organic substrates. The reason for this is that O_2 has a triplet ground state, whose direct interaction with singlet-state organic molecules is a spin-forbidden process. Oxygen-transfer reactions are, however, of importance in two areas:

In biochemistry, oxygenases effect monooxygenations *e.g.* hydroxylations of hydrocarbons, epoxidation of olefins and arenes, lactonization of ketones[1], or dioxygenations *e.g.* the oxidative cleavage of various arenes[2] at room temperature; these reactions occur with high selectivity. Since most oxygenases contain transition metals as their active center, the last few years have seen considerable progress in our understanding of the interaction of dioxygen with transition metal complexes[3], and many models have been found and discussed[4].

The second area is in industry where there is a need for mild, selective, single-step oxidations of hydrocarbons to produce valuable products. Most of the present commercial processes are, however, generally based on radical-chain reactions or heterogeneous catalysis[5]. It would be desirable, therefore, to fix molecular oxygen to transition metal catalysts capable of transferring it selectively to coordinated organic substrates.

The easiest and the cheapest way to activate molecular oxygen is to transform it into organic or inorganic reactive peroxides. This article attempts to rationalize, from a mechanistic point of view, the different ways in which oxygen can be transferred from peroxide reagents to organic substrates. This attempt was necessitated by our study of oxygen transfer from inorganic peroxides which indicated a surprising discrepancy with conventional mechanisms of oxygen transfer from organic peroxides. Thus, we observed that the behavior of dioxirane compounds appeared to be closely related to that of inorganic peroxides. Accordingly, we examined whether such species might be involved as reactive intermediates in oxidations by peroxy acids and other peroxides, and found that such a rationalization can be meaningful.

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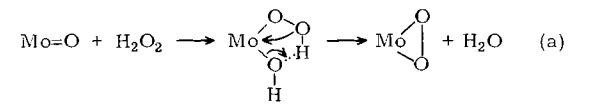
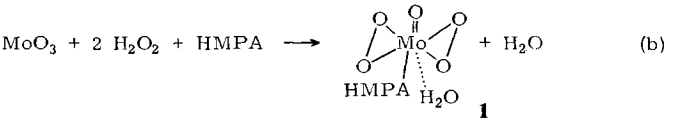
2. Oxygen Transfer from Inorganic Peroxides: Cyclic and Pseudocyclic Peroxymetalation

Our interest in transition-metal peroxide chemistry began in the late 1960s when, after frustrated attempts to isolate stable and well-defined alkylperoxo intermediates in the molybdenum-catalyzed epoxidation of olefins by hydroperoxides[6], we found a new family of peroxomolybdenum and -tungsten complexes of the general formula $MO(O{-}O)_2L^1L^2$ (M = Mo, W; L^1, L^2 = donor ligands such as pyridine, dimethylformamide (DMF), or hexamethylphosphoric triamide (HMPA)). These complexes were obtained from the reaction of molybdenum oxide with hydrogen peroxide in presence of the ligand [reactions (a), (b)][7].



(a)



(b)

1

The X-ray structure determination of complex **1** revealed a pentagonal-bipyramidal structure, with HMPA occupying the equatorial position in the same plane as the two peroxo ligands[8]. **1** is easily dehydrated, producing $MoO_5 \cdot$ HMPA, which is highly soluble in organic solvents. $MoO_5 \cdot$ HMPA was found to be a highly effective reagent for the selective epoxidation of olefins at room temperature in aprotic solvents. The reaction is stereospecific (*cis*-

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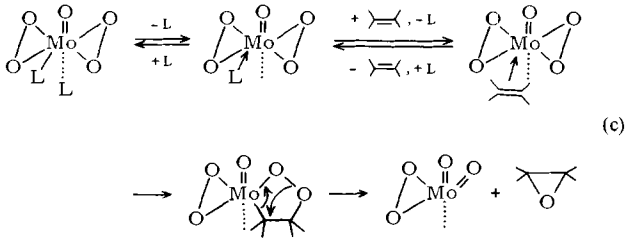
olefins give *cis*-epoxides and *trans*-olefins give *trans*-epoxides) and the reactivity of olefins was found to increase with their nucleophilicity[9]. Kinetic studies, which were later reproduced[10], clearly indicated the reversible formation of an olefin-metal complex in the rate-determining step, followed by irreversible oxygen-transfer to the olefin. NMR spectroscopic monitoring of the reaction indicated that HMPA is displaced from the metal during the oxidation. Furthermore, addition of HMPA to the reaction mixture had a large inhibitory effect on the rate of epoxidation. The peroxidic origin of the transferred oxygen atom was later demonstrated using O^{18} labeling studies[11]. Accordingly, we proposed mechanism (c) to account for the general trends of this oxygen-transfer reaction.



(c)

2 3

The olefin-metal interaction is a pure Lewis acid/Lewis base association, since Mo^{VI} has no d electrons available for back-bonding to the olefin. We would therefore expect the olefin to lose its nucleophilic nature upon coordination, making possible the nucleophilic attack of the coordinated oxygen *via* an intramolecular 1,3-dipolar cycloaddition. The resulting five-membered dioxometallacycle (see **2**) then decomposes by 1,3-dipolar cycloreversion to produce the epoxide and the characterized molybdenum complex **3**. Since the equatorially bound HMPA is displaced by the olefin, it seems likely that the coordinated "dipolarophilic" olefin and the peroxo moiety occupy coplanar adjacent sites.

Although this mechanism disagrees with *Bartlett*'s widely accepted mechanism for the epoxidation of olefins by peroxy acids[12] (see Section 3.1) it is perfectly consistent with the π-σ rearrangement (*cis*-insertion) which occurs in most transition-metal catalyzed transformations of olefins[13]. This cyclic peroxymetalation is similar to the "dimerization" of two coordinated olefins at a metal center involving formation of metallacyclopentanes[14].

Asymmetric epoxidation of simple olefins (*e.g.* propene, *trans*-2-butene) has been achieved stoichiometrically using peroxo molybdenum complexes bearing chiral bidentate ligands[15a]. The X-ray structure determination of $MoO_5 \cdot (+)$-MeCHOH—$CONMe_2$ revealed that the chiral (*S*)-*N*,*N*-dimethyllactamide has bidendate coordination through the carbonyl group at the equatorial position, and through the hydroxyl group at the axial position (Fig. 1)[15b]. The complex was found to epoxidize *trans*-2-butene with enantiomeric excess (e.e.) of up to 35%. Since peroxomolybdenum complexes bearing chiral monodentate ligands exhibit no asymmetric induction, it was assumed that the origin of this asymmetric induction is that *N*,*N*-dimethyllactamide remains axially coordinated *via* the hydroxyl group during the reaction, while the equatorial carbonyl group is displaced by the olefin by analogy to reaction (c) and hence permits formation of the dioxametallacycle[16].

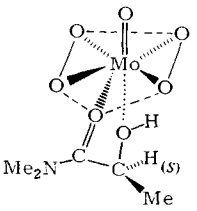
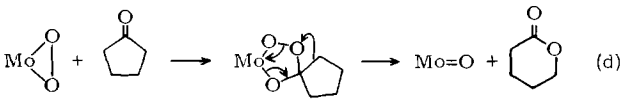


Fig. 1. Structure of the peroxo complex $[MoO(O_2)_2(MeCHOH—CONMe_2)]$.

Peroxo molybdenum complexes have also been shown to α-hydroxylate enolizable ketones, probably *via* epoxidation of the enolate[17], and to cause Baeyer-Villiger lactonization of cyclic ketones *via* formation of five-membered trioxametallacycles [reaction (d)][18].

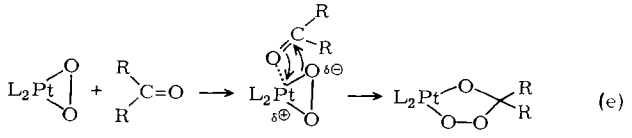


(d)

4

Since the discovery by *Vaska* in 1963 of adducts formed from the reversible addition of dioxygen to $IrCl(CO)(PPh_3)_2$[19] and the characterization of their structure as peroxo complexes[20], a great number of similar transition-metal dioxygen adducts have been reported[3]. Such compounds, *e.g.* $M(PPh_3)_2O_2$ (M = Ni, Pd, Pt) were found to be active catalysts for the oxidation of phosphanes[21] or isonitriles[22], but their use as catalysts for the oxidation of olefins by O_2 led to the same products as those obtained from free-radical chain autoxidations[23].

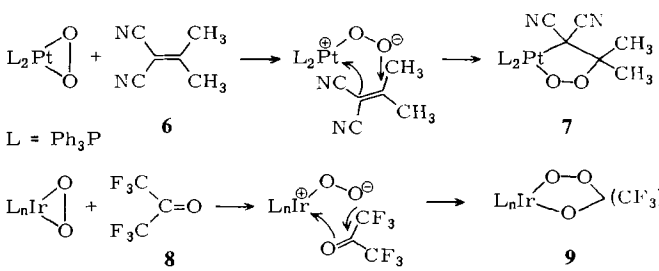
These dioxygen complexes form stable five-membered dioxametallacyclic adducts by reaction either with nucleophilic ketones[24], or electrophilic olefins[25] or fluoroketones[26]. The reaction of $(Ph_3P)_2PtO_2$ with nucleophilic ketones requires coordination of the substrate to the metal prior to the intramolecular nucleophilic attack of the peroxidic moiety at the electrophilic carbon atom bearing the carbonyl group [reaction (e)][24].



(e)

L = Ph_3P 5

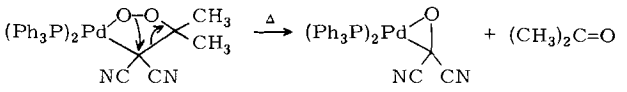
In the case of electrophilic substrates, the peroxo-metallic adduct results from the bimolecular 1,3 dipolar cycloaddition of the peroxo moiety to a cyanoolefin, such as **6**[25b], or a fluoroketone, such as **8**[26].



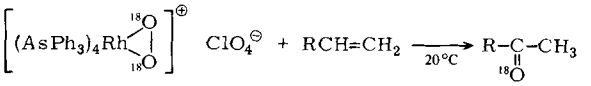
L = Ph_3P 6 7

8 9

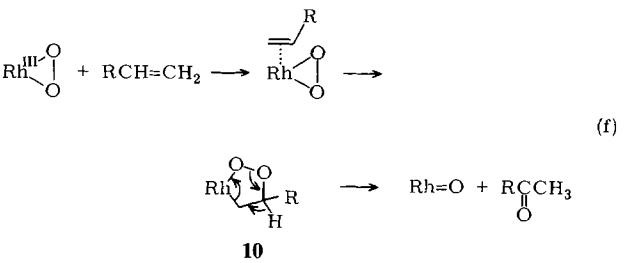
However, the thermal decomposition of the analogously obtained palladium adduct led to oxidative cleavage products instead of to the expected epoxide[25b].



The first evidence for an oxygen-transfer reaction from a dioxygen transition-metal complex to an unactivated olefin was provided by the selective formation of a methyl ketone from ^{18}O-labeled $[(AsPh_3)_4RhO_2]^+ClO_4^-$ and terminal olefins under O_2-free, anhydrous conditions (R = *n*-C_6H_{13}, 85% yield)[27].



This oxygen-transfer reaction was based on the important discovery of *Read et al.*, who found that rhodium complexes such as $RhCl(PPh_3)_3$ were able to promote the co-oxygenation of terminal olefins to afford methyl ketones and of PPh_3 to afford PPh_2O using conditions under which a Wacker-type oxidation (hydroxymetalation of the coordinated olefin by water) was disfavored[28]. Our results on the $RhCl_3/Cu(ClO_4)_2$- or $Rh(ClO_4)_3$-catalyzed oxidation of terminal olefins to methyl ketones by molecular oxygen also led to the conclusion that O_2-activation and O-transfer are involved in reaction (f)[29].



(f)

10

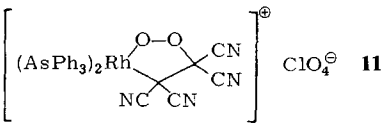
This catalytic reaction occurs under mild conditions with product selectivities, based on the terminal olefin and O_2 consumption, of up to 99%. The reaction is strongly inhibited by the presence of water and is accelerated when a dehydrating agent such as 2,2-dimethoxypropane is added to the reaction medium: competition between olefin and oxygen is observed. Higher O_2 partial pressure inhibits the oxidation of terminal olefins, whereas strongly complexing olefins, *e.g.* styrene or cyclooctene, were found to be less reactive. The reaction is strongly inhibited by ligands, *e.g.* phosphanes or strongly complexing diolefins, *e.g.* 1,5-cyclooctadiene, which compete with the substrate by occupying the vacant coordination sites at the metal.

The product pattern depends on the rhodium-olefin interaction. Terminal and internal olefins, *e.g.* cycloheptene, which form π-complexes with Rh^I, *e.g.* $[RhCl(olefin)_2]_2$, are selectively converted into ketones, whereas olefins which form π-allylic complexes with Rh^{III}, *e.g.* cyclopentene, afford alkenyl ethers *via* oxidative substitution of the olefin by the alcohol used as solvent[29].

The overall catalytic oxidation of terminal olefins to methyl ketones by molecular oxygen has been interpreted as resulting from two reaction steps: an oxygen activation path *via* cyclic peroxymetalation leading to consumption of one oxygen atom and a catalytic Wacker-type hydroxymetalation in which the second atom of O_2 is consumed.

The oxygen activation and transfer reaction depicted in reaction (f) involves coordination of both olefin and the oxygen atom to the same metal center, followed by the Markovnikov-directed peroxymetalation of the coordinated olefin. The decomposition of the dioxarhodacycle **10** occurs *via* a different mode from that of the dioxamolybdacyclo **2**; the less electrophilic nature of rhodium directs the electron transfer toward the β-carbon atom, and induces a β-hydrogen shift.

The dioxarhoda(III) adduct **11** has been isolated from the reaction of $[(AsPh_3)_4RhO_2]ClO_4$ with tetracyanoethylene. $[RhO_2(Ph_2P(CH_2)_2PPh_2)_2]ClO_4$, a peroxo rhodium complex containing bidentate phosphanes as ligands, was found to be inactive with terminal olefins, illustrating the necessity of vacant sites at rhodium[30].

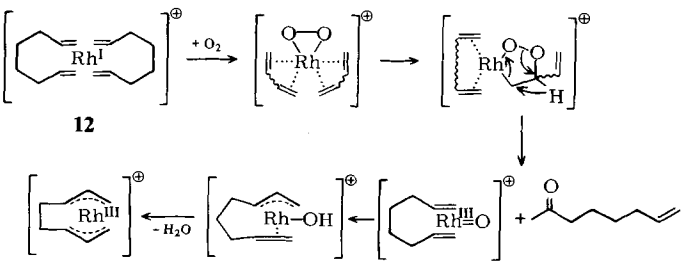


11

Further support for the oxygen activation process in the rhodium-catalyzed oxidation of terminal olefins to methyl ketones comes from the work of *Mares et al.*, who showed that in the presence of both $^{16}O_2$ and $H_2{}^{18}O$, 1-octene was oxidized to unlabeled 2-octanone using $RhCl(AsPh_3)_3$ as catalyst[31].

As shown in reaction (f), the intermediate **10** can be obtained from the reaction of a peroxorhodium(III) complex with the olefin. It may also result from the reaction of an olefinrhodium(I) complex with dioxygen. We succeeded in isolating $[Rh^ICl(1,7\text{-octadiene})]_2$, which reacted with $AgBF_4$ in the presence of 1,7-octadiene to afford the cationic complex **12** containing only olefinic ligands at Rh^I.

In anhydrous isopropanol, and even in the presence of excess 1,7-octadiene, **12** absorbs 1 mol of dioxygen per mol of rhodium, producing *ca.* 1 mol of 7-octen-2-one and 1 mol of water. Since no acetone was formed, we assume that the hydrogen source for H_2O was the olefin itself; the π-allylic complex of Rh^{III} is formed by opening the dioxarhodacyclo by a β-hydrogen shift.



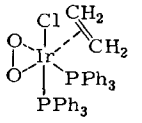
12

Anion: $BF_4^\ominus$

In the presence of 1 equivalent of HBF_4 and a large excess of 1,7-octadiene, more than 1 mol of O_2 was absorbed per mole of rhodium, whereas neither water nor acetone (from isopropanol used as solvent) were produced. Under these conditions, both atoms of O_2 were incorporated into 2 mol of the olefins, and the production of 7-octen-2-one is slightly catalyzed. This catalytic reaction interpreted as a peroxymetalation step followed by a Wacker-type hydroxymetalation of the coordinated olefin (*vide supra*).

It therefore appears that peroxo molybdenum complexes and dioxygen rhodium complexes exhibit similar behavior in transferring oxygen to olefins. Both involve coordination of the olefin to the metal, followed by intramolecular 1,3-dipolar cycloperoxymetalation of the substrate. The difference in the nature of the resulting oxygenated products (epoxides, ketones, or oxidative cleavage compounds) is due to the different mode of decomposition of the dioxametallacycle, and depends on the electrophilicity of the metal and the nature of the substrate. Such a directed transfer of oxygen to unactivated olefins cannot occur directly from other peroxo complexes, since this requires special coordination possibilities *i.e.* coplanar adjacent location of the substrate and the peroxy ligands at the metal. This is the case for $M(PPh_3)_2O_2$ complexes (M = Ni, Pd, Pt) as well as iridium complexes **13** containing both O_2 and ethylene[32].

$$[IrCl(C_8H_{14})_2]_2 + 2\ PPh_3 + C_2H_4 + O_2 \longrightarrow$$



13

This is also the case for some early peroxo transition-metal complexes having 18 electrons in the valence shell, *e.g.* $(C_5H_5)_2NbO_2Cl$[33] or a porphyrin ring, *e.g.* (tpp)$Mo(O_2)_2$[34] or (tpp)TiO_2[35] (tpp = tetraphenylporphyrin).

In the last mentioned oxygen-transfer reactions from peroxo complexes, the primary oxygen source is generally H_2O_2 in the case of early transition-metal complexes, or O_2 in the case of group VIII metals. However, there is another class of metal-catalyzed oxidations in which the reactive intermediates are M—O—O—R or M—O—O—H species. These involve molybdenum-, boron-, or aluminum-catalyzed epoxidation of olefins by alkyl hydroperoxides and palladium-catalyzed oxidation of terminal olefins to methyl ketones by alkyl hydroperoxides or hydrogen peroxide.

In the palladium-catalyzed ketonization of terminal olefins by *tert*-butyl hydroperoxide, our attempts to isolate the reactive intermediates led to the successful preparation of stable, well-defined *tert*-butyl peroxo palladium carboxylates of general formula $[Pd(RCO_2)(OO\mathit{t}Bu)]_4$ **14**; the structure of the derivative **14a** (with $R = CCl_3$) is depicted in Figure 2[36].

These palladium alkyl peroxides were found to be very efficient reagents for the selective transformation of terminal olefins into methyl ketones in anhydrous non-basic organic solvents at room temperature. The reactivity of these complexes toward terminal olefins decreases in the order $R = CF_3 > C_5F_{11} > CCl_3 > CH_3$. The reaction of *tert*-butyl

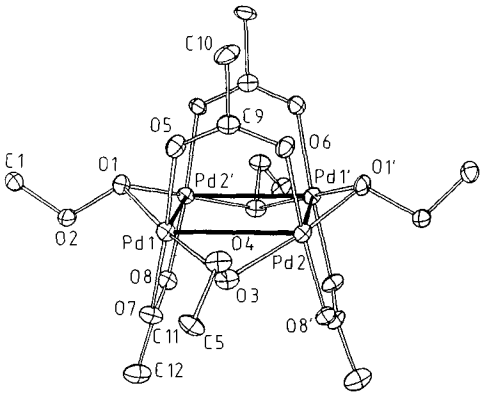
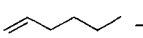
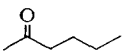


Fig. 2. Molecular structure of the tetrameric palladium complex $[Pd(Cl_3CCO_2)(OO\mathit{t}Bu)]_4$ **14a** in the crystal. In the interests of clarity, chlorine atoms and methyl groups have been omitted.

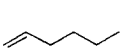
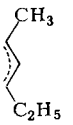
peroxo palladium trifluoroacetate **14b** with 1-hexene has been shown to proceed in two steps: oxygen transfer from the complex to the olefin affording the methyl ketone and the *tert*-butoxy palladium complex **15b**; rapid substitution of the *tert*-butoxy group on the metal by the olefin, gives rise to *tert*-butanol and a π-allylic complex [reaction (h)].

$$CF_3CO_2Pd{-}OO\mathit{t}Bu + \text{  } \xrightarrow{k_1}$$

14b (g)

$$CF_3CO_2Pd{-}O\mathit{t}Bu + \text{  }$$

15b

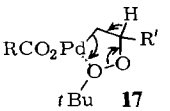
$$\textbf{15b} + \text{  } \xrightarrow{k_2} CF_3CO_2Pd\text{  } + \mathit{t}BuOH \quad \text{(h)}$$

$k_2 \gg k_1$

Only terminal olefins can be effectively transformed by the palladium reagent **14b**. Internal olefins produce the π-allylic complex directly, liberating *tert*-butyl hydroperoxide. A consideration of the general trends of this oxidation led us to propose the mechanism depicted in (i) for the oxygen-transfer reaction.

$$RCO_2Pd{-}OO\mathit{t}Bu \xrightarrow{+\ \text{ }} RCO_2Pd{-}OO\mathit{t}Bu \longrightarrow$$

14 **16** (i)



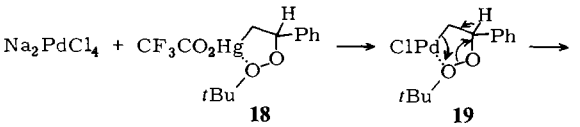
$RCO_2Pd{-}O\mathit{t}Bu$ +

17

The first step consists of coordination of the terminal olefin to palladium produces complex **16**. Intramolecular nucleophilic attack of the *t*BuOO group at the coordinated electrophilic olefin constitutes the "*cis*-peroxypalladation" step and gives rise to the formation of the five-membered pseudocyclic intermediate. Decomposition of **17** occurs by rupture of the O—O bond, followed by a β-

hydrogen shift, producing the methyl ketone and the *tert*-butoxy palladium complex **15**. This reaction step is similar to that of the dioxarhodacycle **10**.

It is noticeable that the pseudocyclic intermediate **17** strongly resembles the stable alkyl peroxymercury complex **18** prepared from the reaction of *t*-BuOOH with an olefin in the presence of mercury(II) carboxylate[37]. The recent X-ray structure determination of an adduct of this type, BrHg—CH(Ph)CH(Ph)—OO*t*Bu, has clearly shown the existence of an interaction between mercury and the oxygen atom adjacent to the *tert*-butyl group, forming the five-membered pseudocyclic structure[38]. Owing to the easy transmetalation of organomercury compounds with palladium chloride[39], we expected that the reaction of Na_2PdCl_4 with **18** would produce the unstable pseudocyclic intermediate **19**, which subsequently decomposes to afford the methyl ketone. Indeed, acetophenone was formed in 95% yield from this reaction at 20 °C in tetrahydrofuran (THF), together with insoluble $HgCl_2$[36].



18 **19**

$$PhCCH_3 + HgCl_2 + CF_3CO_2Na + ClPdO\,tBu$$

Methyl ketones can be produced catalytically when an excess of *t*-BuOOH is used for regenerating **14** from the resulting alkoxy complex **15** [reaction (i)]. In order to avoid formation of a π-allylic complex and hence lower selectivities, a large excess of *t*-BuOOH with respect to the olefin is required[40].

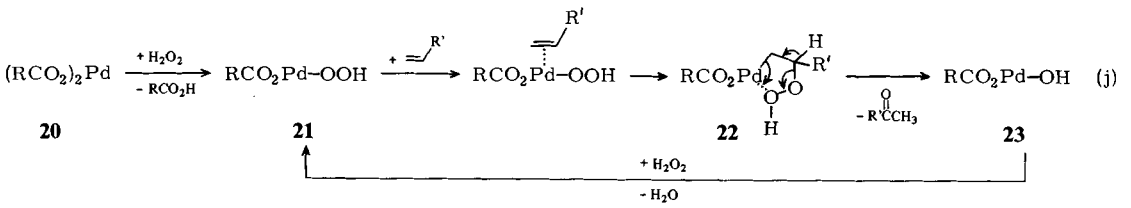
$$tBuOOH + RCH{=}CH_2 \xrightarrow{Pd(RCO_2)_2\ \mathbf{20}} tBuOH + RCCH_3 \quad (O)$$

We have also recently found that palladium(II) carboxylates are effective catalysts for the selective oxidation of terminal olefins to methyl ketones by H_2O_2[41].

$$RCH{=}CH_2 + H_2O_2 \xrightarrow{Pd(RCO_2)_2\ \mathbf{20}} RCCH_3 + H_2O \quad (O)$$

This reaction is best carried out between 20 and 80 °C in solvents such as *tert*-butanol or acetic acid. The best catalysts were found to be **20** or **14** (R = CH_3 or CF_3), whereas palladium complexes containing strongly coordinating bidendate ligands were found to be inactive in *tert*-butanol. For sufficiently high conversion of the substrate (>90%) to methyl ketone, a large excess of H_2O_2 with respect to the olefin is required (H_2O_2 : olefin ≧ 3 : 1).

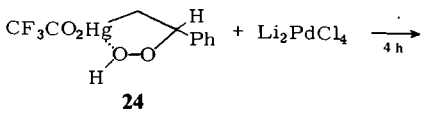
As expected, only terminal olefins, such as 1-hexene, 1-octene, 1-dodecene, and allyl acetate were oxidized to the corresponding methyl ketones with adequate conversion and selectivity (up to 90%). The efficiency of the catalyst is very high: one mol of $Pd(OAc)_2$ was found to convert about 400 mol of 1-octene into 2-octanone per hour (80 °C, olefin : $Pd(OAc)_2$ = 1500 : 1, H_2O_2 : 1-octene = 5 : 1). Partial decomposition of H_2O_2 was found to occur during the reaction, and *ca.* 2—3 mol of H_2O_2 were consumed per mol of 1-octene transformed. Oxidation of 1-octene in *tert*-butanol by $H_2{}^{16}O_2$ catalyzed by $Pd(OAc)_2$ in presence of a large excess of $H_2{}^{18}O$ resulted in formation of only unlabeled 2-octanone. This therefore indicates that the oxygen source for ketone formation is only H_2O_2, and *not* water as in the Wacker process. The following mechanism (j), similar to that previously shown for reaction (i), was suggested[41].



20 **21** **22** **23** (j)

As reactive species, this mechanism involves the hydroperoxide **21** resulting from the exchange of one carboxylate group of **20** at palladium. This compound transfers one oxygen atom to the coordinated olefin and, *via* a hydroperoxypalladation corresponding to mechanism (i), yields the methyl ketone and the palladium hydroxide **23**. Species **21** is regenerated from **23** by reaction with H_2O_2, liberating water. A large excess of H_2O_2 is necessary in order to avoid Wacker-type hydroxypalladation of the olefin by **23**, π-allyl complex formation, and to compensate for the decomposition of the unstable palladium hydroperoxide **21** (evolution of O_2). Despite many attempts, the isolation of such palladium hydroperoxide species was unsuccessful. However, there are several indirect indications of the involvement of such intermediates in the ketonization of terminal olefins:

1) The reaction of the stable hydroperoxyalkylmercury compound **24**[42] with Li_2PdCl_4 (20 °C, THF) produced acetophenone in 85% yield[43].



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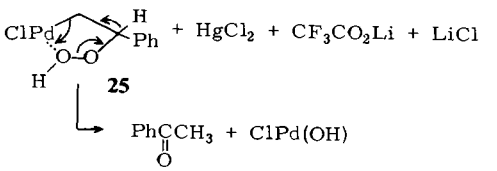
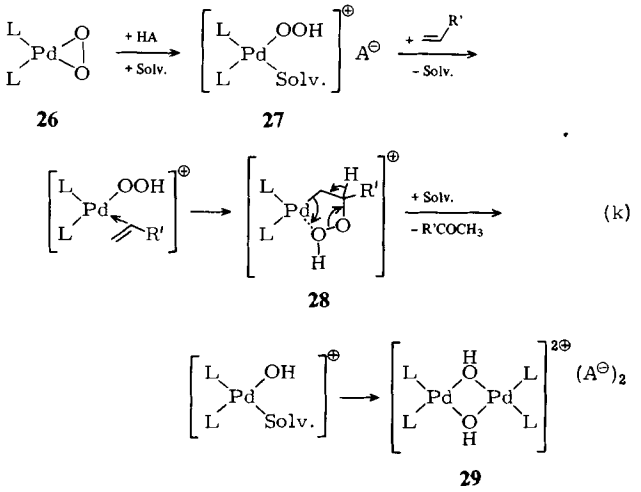


25

2) Cation **27** was generated by protonation of **26** by one equivalent of a strong noncoordinating acid, such as CH_3SO_3H, in a CH_2Cl_2/1-octene solution and afforded 2-octanone (50% yield based on palladium) together with Ph_3PO (36%). As shown by reaction (k), protonation of the

peroxo group in the inactive complex **26** creates a vacant site (**27**), which is occupied by a solvent molecule[43], and allows complexation of the olefin prior to the hydroperoxypalladation. The di-μ-hydroxy complex **29** has been isolated (A = BF_4). The addition of an acid with a strongly coordinating anion, such as CF_3CO_2H, results in almost complete inhibition of oxidation, since now the vacant site S is preferentially occupied by the CF_3CO_2 group, impeding coordination of the olefin. When the oxidation of 1-octene was carried out in presence of excess $H_2{}^{18}O$ only unlabeled 2-octanone was produced, indicating that the oxygen source for ketone formation is not water but molecular oxygen bound in the complex.



26 **27** **28** **29**

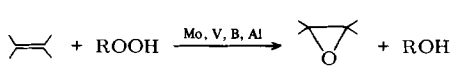
L = PPh_3, Solv. = CH_2Cl_2, $A^{\ominus}$ = $CH_3SO_3^{\ominus}$, $BF_4^{\ominus}$

The results indicate that under these conditions the internal *cis*-hydroperoxypalladation of the coordinated olefin prevails over external *trans*-hydroxymetalation by water (Wacker process). They also illustrate an additional possibility for oxygen activation and transfer to olefin at the coordination sphere of a metal, involving one monoanionic OOH group adjacent to a coordinated olefin, whereas in the case of the rhodium complex [see reaction (f)] the peroxo dianion adjacent to a vacant coordination site was required.

Platinum hydroperoxides, —Pt—OOH, obtained in the same way from the protonation of $(PPh_3)_2PtO_2$ by CH_3SO_3H, were found to be unreactive toward terminal olefins, probably due to the lower coordinating ability of platinum compared to palladium[43].

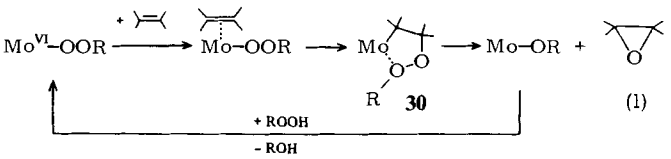
It therefore appears that oxygen can easily be transferred to olefins from group VIII dioxygen metal complexes, provided a suitable coordination site for the coordination of the olefin exists (rhodium complexes), or is liberated after protonation of the peroxo group (palladium complexes). If this condition is not fulfilled, no oxygen transfer to olefin can occur.

The concept of pseudocyclic peroxymetalation has also proved useful for interpreting the mechanism of the epoxidation of olefins by alkyl hydroperoxides catalyzed by molybdenum, vanadium, boron, and aluminum.

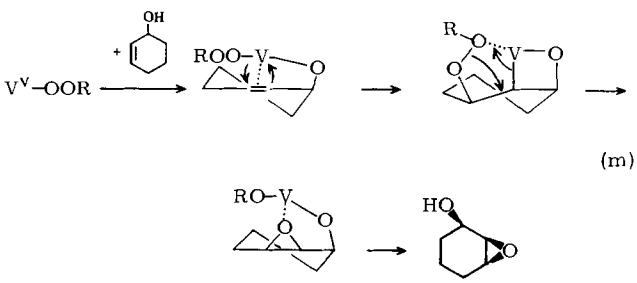


The molybdenum-catalyzed reaction has been developed on a large scale by Halcon for the production of propylene oxide by oxidation of propylene with *tert*-butyl hydroperoxide[45]. Many characteristics of this reaction are similar to those of the epoxidation of olefins by peroxo molybdenum complexes, *i.e.* high stereoselectivity and retention of configuration, increasing reactivity with increasing nucleophilicity of the olefin, and strong inhibition by coordinating σ-donor solvents and ligands[46]. Furthermore, the reaction is inhibited by the coproduct alcohol. Although not yet fully characterized, the reactive intermediates of this reaction have been shown by ^{18}O labeling studies to be the alkyl peroxo molybdenum complexes obtained by displacement of a ligand on Mo^{VI} by hydroperoxide[6].

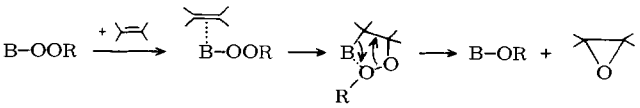
The suggested mechanism (l) satisfactorily accounts for the general trends of this catalytic oxidation.



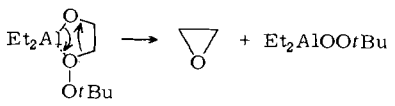
This involves coordination of the nucleophilic substrate to Mo^{VI} followed by a pseudocyclic alkyl-peroxymetalation of the coordinated olefin. The intermediate **30** strongly resembles the cyclic intermediate **2** postulated for the epoxidation of olefins by MoO_5·HMPA [reaction (c)]; **30** decomposes in the same way to give the epoxide and the molybdenum alkoxide. The coordinatively rigid structure of **30** also accounts for the high stereoselectivity of this reaction, exemplified by the vanadium-catalyzed epoxidation of allylic alcohols, which yields *syn*-epoxides almost quantitatively [reaction (m)][47].



In reactions (c) and (l) the metal-olefin association preceding the peroxymetalation reaction is a pure Lewis acid/Lewis base interaction, since Mo^{VI} and V^{V} are d^0 complexes. It would therefore be expected that compounds having alkylperoxy groups bonded to a Lewis acid center should be active for the epoxidation of olefins. This is indeed found for boron compounds, which are active as catalysts for the epoxidation of olefins by alkyl hydroperoxides[48]. Boron tris(alkyl peroxides) $B(OOR)_3$ have been shown to stoichiometrically epoxidize alkenes, presumably through alkyl-peroxyboration of the double bond.

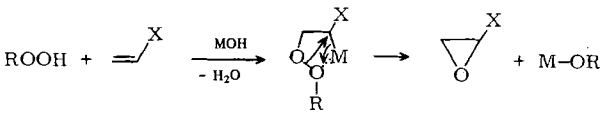


Aluminum compounds such as $(t\mathrm{BuO})_3\mathrm{Al}$ have also been shown to catalyze the epoxidation of olefins by alkyl hydroperoxides, and this reaction is also particulary selective for the transformation of allylic alcohols into *syn*-epoxides[50]. Related to the mechanism of this aluminum-catalyzed epoxidation is the decomposition of the aluminum compound **31** to give ethylene oxide[51].



31

Five-membered "pseudocyclic" peroxides such as **32** have also been assumed to be involved as reactive intermediates in the epoxidation of electron-poor olefins by H_2O_2 or ROOH in presence of alkali[52].



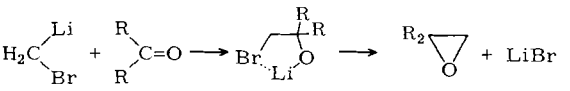
32

R = H or *tert*-alkyl

X = acceptor group. Reactivity of the olefin decreases along the series $X = NO_2 > SO_3R > CHO > COR > COOR > CN$

M = alkali metal. Activity of the base increases in the order $KOH < NaOH < LiOH$.

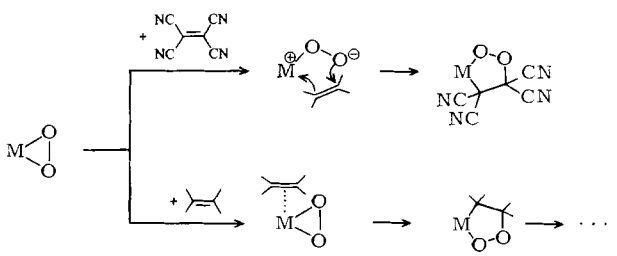
Epoxides have also been obtained from the reaction of carbonyl compounds with α-bromomethyllithium, presumably *via* decomposition of the pseudocyclic intermediate **33**[53].



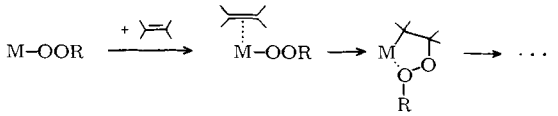
33

We can summarize the results from Section 2 as follows:

1) Peroxo metal complexes behave as 1,3-dipolar reagents $M^+—O—O^-$. The peroxo group reacts either bimolecularly with electrophilic substrates such as tetracyanoethylene or hexafluoroacetone, or else monomolecularly with coordinated nucleophilic olefins or ketones which become electrophilic in the metal-coordinated form. In both cases, the primary product is a cyclic five-membered dioxametallacycle. This reaction is called cyclic peroxymetalation.



2) Alkylperoxo or hydroperoxo metal complexes react with olefins *via* intramolecular nucleophilic attack of the —OOR or the —OOH group, respectively, at the coordinated olefin, which has become electrophilic due to coordination to the metal. As for cyclic peroxymetalation, this reaction obeys the general π-σ rearrangement procedure (*cis*-insertion) occurring in most transition metal-catalyzed transformations of olefins[13]. The primary product is a five-membered "pseudocyclic" alkyldioxyethylmetal compound.



3) In intramolecular cyclic and pseudocyclic peroxymetalations, the rate-determining step is generally the coordination of the olefin or the ketone to the metal. This requires the presence on the metal of vacant coordination sites adjacent to the peroxide group. Hence, increasing the electrophilicity of the metal and increasing the nucleophilicity of the substrate favor the reaction, whereas the presence of strongly coordinating ligands or basic solvents, in contrast, inhibit complexation of the substrate and, hence, the reaction.

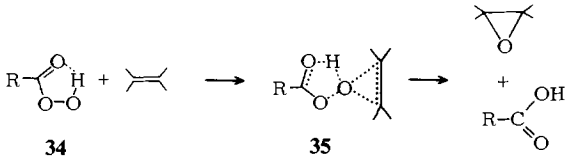
4) The decomposition of the cyclic and pseudocyclic peroxometallic adducts occurs *via* a concerted 1,3-dipolar cycloreversion. The nature of the products depends on the metal and the substituents on the substrate. With pure Lewis acids or d^0 transition-metals containing peroxide groups, epoxides are preferentially obtained from olefins, and esters result from the Baeyer-Villiger oxidation of ketones. In the case of less electrophilic group VIII metals predominantly β-hydrogen shift occurs; methyl ketones result from the oxidation of terminal olefins, whereas oxidative cleavage occurs with some electrophilic olefins.

5) Peroxymetalation requires the activation of both dioxygen and olefin at the same metal center: a) Oxygen can be used as a peroxide (H_2O_2 or ROOH), or can be reduced to a peroxide by donation of two electrons from the metal (*e.g.* Rh or Pd); b) the olefin loses its nucleophilic character upon complexing to the metal and becomes electrophilic, making possible intramolecular nucleophilic attack by the peroxide.

3. Oxygen Transfer from Organic Peroxides: 1,3-Dipolar Cycloaddition of Dioxiranes

3.1. Oxidation by Peroxy Acids

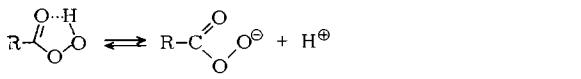
The mechanistic interpretation of organic oxidation reactions has long been, and still is, dominated by the concept of "electrophilic oxygen" characterizing the nature of the transferred oxygen atom in oxidations of organic substrates by peroxy acids[54]. The "butterfly mechanism" of the epoxidation of olefins by peroxy acids, first proposed by *Bartlett* in 1950, illustrates this concept [reaction (n)][55].



(n)

34 35

This mechanism involves nucleophilic attack of the olefin at the terminal "electrophilic" oxygen atom of the hydroperoxide group, followed by decomposition of the intermediate **35** into the epoxide and the carboxylic acid. Although this mechanism has long been very useful for interpreting many epoxidation reactions[56], and has recently received theoretical support[57], it suffers from the fact that the electrophilic nature of the transferred oxygen atom has never been clearly established. On the contrary, it would be expected that peroxy acids with acidity constants of pK = 3.7 (R = CF_3) or pK = 7.6 (R = CH_3) are dissociated in solution as shown in (o), and that a negative charge is located on the terminal oxygen atom.

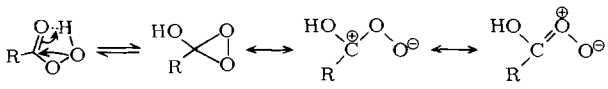


(o)

34

The rate of epoxidation is largely enhanced by the acidity of the peroxy acid, which increases with the introduction of electron-withdrawing substituents[58]. Furthermore, *Hjelmeland* and *Loew* have established by *ab initio* and semi-empirical MO calculations that neither of the peroxidic oxygen atoms of peroxy acids is electrophilic[59]. This makes the association (**35**) between olefin and peroxy acid unlikely in the sense of charge-transfer interactions. A nucleophilic attack on peroxy acids should therefore more probably occur at the electrophilic center of the molecule, *i.e.* the carbon of the CO_3H group, as shown by the hydrolysis by $H_2{}^{18}O$[60].

An alternative mechanism suggested later by *Kwart et al.* considers the intramolecularly hydrogen-bonded peroxy acid as a potential hydroxy-substituted dioxirane [reaction (p)][61,62].

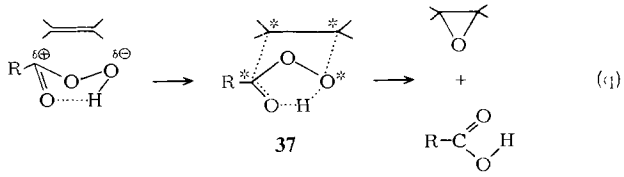


(p)

34 36a 36b 36c

The existence of peroxymethylene compounds **36** was first postulated by *Criegee* in 1949 for the ozonolysis of alkenes[63]. Although they have not yet been isolated, cumulative evidence has been provided which supports their involvement in many oxidation reactions. The dioxirane species **36a** has been identified in the gas-phase reaction of ozone with ethylene[64], and has been shown by theoretical studies to be far more stable than the zwitterion **36b**, the *cis*- and *trans*-carbonyl oxide **36c**, or the corresponding diradical[65]. Hence, dioxiranes are the products expected from the pericyclic rearrangement of peroxy acids **34** and from decomposition of the primary ozonides (see Section 3.3.3).

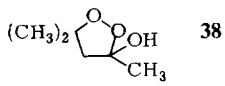
Kwart's epoxidation mechanism (q) involves the 1,3-dipolar cycloaddition of the peroxy acid in its zwitterionic form **36b** to the double bond, forming a cyclic peroxide **37** which decomposes to epoxide and carboxylic acid[62].



(q)

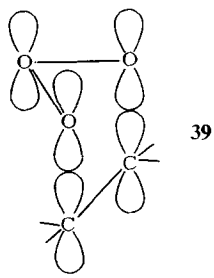
37

Since 1,2-dioxolanes such as **38** are unexpectedly stable, and upon thermolysis at 100 °C give only minor amounts of epoxide, it was concluded that this type of dioxolane never actually forms, but that "the very act of approach to bond formation produces rearrangement to epoxide by virtue of the conformation accomodation that produces O—O bond rupture, without intermediate formation of the 1,2-dioxolane (which would be the hypothetical nonplanar, stable product of the 1,3 dipolar cycloaddition)"[62].



38

The suggested alternative transition state **37** has been shown by molecular orbital considerations to require the coplanity of four (*) centers. It is worth pointing out that this envelope conformation is similar to the geometry of transition state **39** postulated for the *supra-supra* addition of ozone (4π) to olefins (2π)[66].



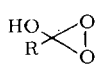
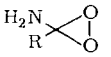
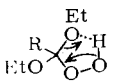
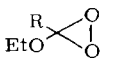
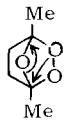
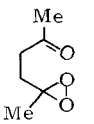
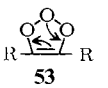
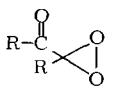
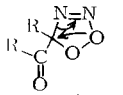
39

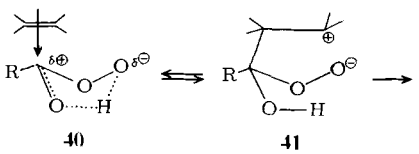
It should be recalled that coplanity of the peroxo ligand and the olefin is also required in the epoxidation of olefins by $MoO_5 \cdot$HMPA [reaction (c)].

The similarity between the mechanism of the epoxidation of olefins by peroxy acids and $MoO_5 \cdot$HMPA is further emphasized if we assume that the rate-determining step consists in the formation of a charge-transfer π-complex between the nucleophilic olefin and the electrophilic carbon atom of the peroxymethylene **36** prior to the nucleophilic attack of the terminal peroxidic oxygen atom at the "coordinated" electrophilic olefin (**40**) or the positively charged C atom (**41**) [reaction (r)].

This would explain why acceptor substituents in the peroxy acid increase the electrophilic nature of the C atom of the zwitterion, favor the formation of a charge transfer complex, and therefore increase the rate of epoxidation. Likewise, electron-rich olefins are more easily "coordinated", and are therefore more readily epoxidized[56].

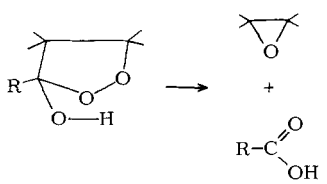
Table 1. Organic peroxide reagents. A: Olefin epoxidation; B: Baeyer-Villiger oxidation of ketones to esters; C: Hydroxylation of hydrocarbons; D: Oxidation of organic sulfur and nitrogen compounds; E: Conversion of carbonyl compounds into ozonides.

Educts or Synthesis	Normal form	Dioxirane form	Reactivity
$RCO_2H + H_2O_2 \xrightarrow{H^\oplus}$	**34**	 **36a**	Arbitrary R: A, B, D[56] R = CF_3, 4-NO_2-C_6H_4: C[127]
$RC{\equiv}N + H_2O_2 \longrightarrow$	**44**	 **45**	R = CH_3, CCl_3, Ph: A[128]
$R_2C{=}O + H_2O_2 \longrightarrow$	**46**	$\xrightarrow[+H_2O]{-H_2O}$ **47**	**a**, R = CF_3: A[78], B[77], D[79] R = CCl_3: A[81] R = Triazolyl: A[82]
$RC(OEt)_3 + H_2O_2 \longrightarrow$		$\xrightarrow[+EtOH]{-EtOH}$  **50**	R = Me: A[84]
$^1O_2$- or O_3-oxygenation	 **51**	$\rightleftharpoons$  **52**	A, B, D[85]
$R{-}C{\equiv}C{-}R + O_3 \longrightarrow$	 **53**	 **55**	with O_3: R = Me: A[86] with $^1O_2$: R = Ph: B, D[87]
$R{-}C(=O){-}C(=N_2){-}R + {}^1O_2 \longrightarrow$	 **54**	$-N_2$	



40 **41**

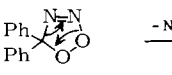
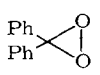
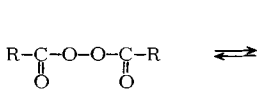
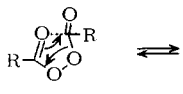
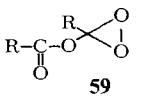
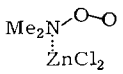
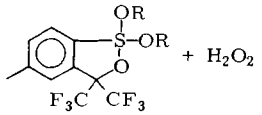
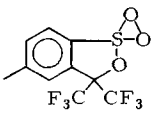
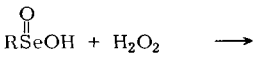
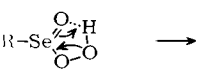
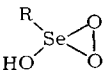
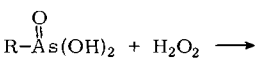
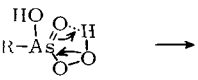
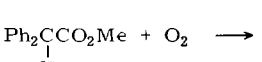
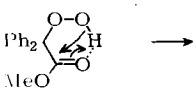
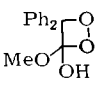
(r)



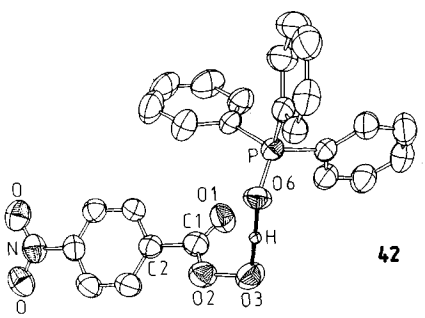
It is expected that the olefin would lose its nucleophilic nature upon complexation, enabling nucleophilic attack by the terminal oxygen atom, which should be Markovnikov directed. This is consistent with the results of measurements of secondary deuterium isotope effects carried out by *Hanzlik et al.* These studies revealed a clear distinction between the α- and β-positions of the olefin in the transition state[67]. The determination of the Hammet constants for epoxidation with peroxy acids[68,56] yielded a negative value of ρ and a large σ^+ contribution for olefins, and a positive ρ value for peroxy acids. These results are consistent with a charge separation in the transition state, which is partially positive on the olefinic moiety and partially negative on the peroxy acid moiety[67]. Recent kinetic studies of epoxidation with peracids in presence of nitrogen bases have also led to the conclusion that a charge-transfer complex between the peroxy acid and the olefin is formed prior to epoxide formation[69].

Solvent effects in peroxy acid epoxidations can also be accounted for by formation of a charge-transfer complex between peroxy acid and olefin. Basic solvents or ligands such as DMF, amine, phosphane, or arsane oxides inhibit epoxidation by disrupting the intramolecular hydrogen-bonded structure of the peroxy acid, thus preventing formation of the dioxirane species[70]. Stable crystalline complexes between peroxy acid and such ligands have been isolated[71]; the structure of the adduct **42** between *p*-nitro-

Table 1. (Continuation) Organic peroxide reagents. A: Olefin epoxidation; B: Baeyer-Villiger oxidation of ketones to esters; C: Hydroxylation of hydrocarbons; D: Oxidation of organic sulfur and nitrogen compounds; E. Conversion of carbonyl compounds into ozonides.

Educts or Synthesis	Normal form	Dioxirane form	Reactivity
$Ph_2C{=}N_2 + {}^1O_2$		 **56**	A[129], C[90], D[87], E[89]
 R = Aryl		 **59**	A[92]
$Me_2N{-}N{=}N{-}NMe_2 + O_2$	$\xrightarrow{ZnCl_2}$	 **60**	A[93]
 **61**	$\xrightarrow{-2\,ROH}$	 **62**	A, D[94]
 R = Aryl	 **64**		A[96], B[97]
	 **65**		A, B[98]
	 **66**	 **67**	A[100]

peroxybenzoic acid and triphenylphosphane oxide has been determined by X-ray crystallography and is reproduced in Figure 3[172].



42

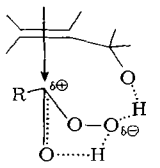
Fig. 3. Molecular structure of the complex **42** from *p*-nitroperbenzoic acid and triphenylphosphane oxide in the crystal [72].

The relatively lower rate of epoxidation in π-electron donor solvents, *e.g.* aromatic hydrocarbons, in comparison with in chlorinated non-aromatic solvents[56,57] could be explained by competition between olefin and solvent for the formation of charge-transfer π-complexes with the peroxy acid.

The smaller difference in reactivity of norbornene and cyclohexene toward peroxy acids ($k_1/k_2 = 1.2$) than toward 1,3-dipolar reagents such as phenyl azide ($k_1/k_2 = 6500$) has been used as an argument against Kwart's mechanism [five-membered transition state, see reaction (q)] and in favor of Bartlett's mechanism [three-membered transition state see reaction (n)][74,75].

These results, however, are consistent with mechanism (r). Since the rate-determining step is the formation of the π-complex **40** (three-membered transition state), the olefin reacts more according to its nucleophilic nature uninfluenced by its strain energy; this first becomes important in the next non-rate determining 1,3-dipolar cycloaddition.

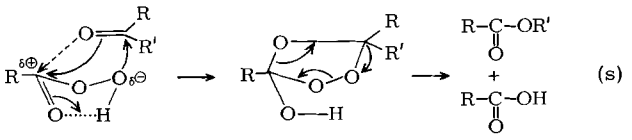
The directing effect of hydroxy, carboxy and carboxylate substituents on the olefin for formation of *cis*-epoxides[56] can also be interpreted by the modified Kwart mechanism (r), assuming the existence of a cyclic hydrogen-bonded intermediate **43**.



43

Hence, a modified Kwart mechanism, *i.e.* formation of a charge-transfer π-complex between the olefin and the peroxy acid as the rate-determining step followed by a 1,3-dipolar epoxidation is in accord with most of the data concerning this reaction.

The same mechanism would also be suitable for interpreting the Baeyer-Villiger oxidation of carbonyl compounds to esters by peroxy acids[76]. Great similarity exists

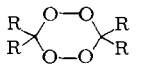


(s)

between this mechanism (s) and the formation of stable metal ozonides in the reaction of peroxo platinum complexes with ketones [reaction (e)], this also applies to the Baeyer-Villiger lactonization of cyclic ketones by peroxo molybdenum complexes [reaction (d)].

oxide **46a** which can be converted into bis(trifluoromethyl)dioxirane **47a** upon elimination of water (Table 1).

The formation of **47a** corresponds to the reaction of transition-metal oxides with H_2O_2 to form peroxo complexes **1** and is favored by the electrophilic character of the carbon atom of the dioxirane ring, caused by the electron-attracting effect of the two CF_3 groups. Dimeric (or trimeric) cyclic peroxides such as **48**, which can formally be treated as stable dioxirane oligomers, are commonly obtained from the reaction of carbonyl compounds with H_2O_2[83].

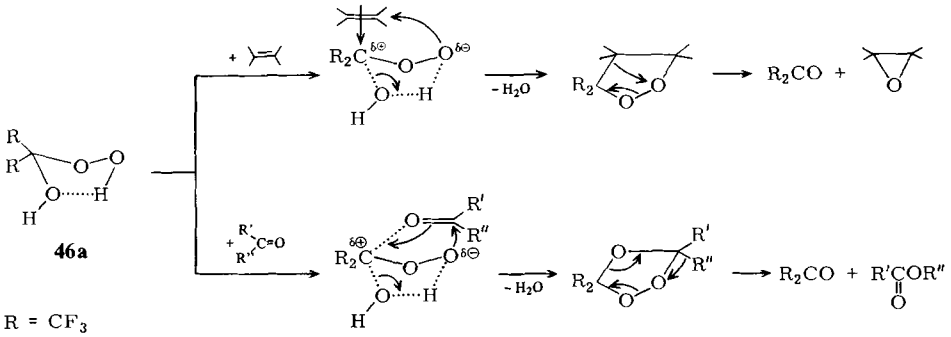


48

Oxygen transfer from a dioxirane (*e.g.* **47a**) to nucleophilic substrates such as olefins or ketones could, therefore, occur in an analogous way to that shown in mechanism (r) (rearrangement of peroxy acids).

It is noteworthy that the combination of alkyl hydroperoxides with hexafluoroacetone to afford **49** does *not* epoxidize olefins[78a], since dioxirane formation cannot occur!

The formation of epoxidation reagents from the reaction of H_2O_2 with dehydrating orthoesters such as



3.2. Oxidation by Dioxiranes

One of the most common striking features of the organic peroxides described in Table 1 is their ability to generate dioxiranes by sigmatropic rearrangement, which often results in the loss of water, alcohol, or N_2. Various oxygen sources are suitable for these dioxiranes, *i.e.* $^3O_2$, $^1O_2$ (singlet oxygen), ozone or hydrogen peroxide. Most of the reagents in Table 1 contain electron-acceptor substituents. All these peroxide species behave as oxidizing agents: they epoxidize olefins, transform ketones into esters (Baeyer-Villiger oxidation), oxidize organic sulfur and nitrogen compounds, and in part, hydroxylate nucleophilic C—H groups.

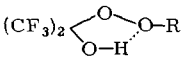
The use of an anhydrous mixture of hexafluoroacetone and hydrogen peroxide as a selective oxidant for the Baeyer-Villiger oxidation of ketones was first reported by *Chambers* and *Clark*[77]. Later it was shown to selectively epoxidize olefins[78], convert amines and sulfides into their corresponding oxides[79], and oxidize aldehydes to carboxylic acids[80]. Hexachloroacetone[81] and carbonylditriazole[82] in the presence of H_2O_2 were also found to be suitable for the epoxidation of olefins. The solvent is generally anhydrous CH_2Cl_2. Although it has not yet been isolated, the reactive species is most probably the hydroxyhydroper-

$MeC(OEt)_3$[84], might also be attributed to the generation of a reactive ethoxy-substituted dioxirane species **50** (Table 1).

Reactive dioxirane species may also be synthesized from O_2 or O_3 oxygenations in aprotic solvents. Epidioxyfurans such as **51** have been shown to cause epoxidation of olefins and Baeyer-Villiger lactonization of ketones, presumably *via* the transient formation of the intermediary dioxirane **52**[85].

Ozonolysis of alkynes produces reactive intermediates capable of epoxidizing olefins[86]. It has been suggested that these reactive intermediates are probably the acyl-substituted dioxiranes **55** resulting from the rearrangement of the primary ozonide **53**[86] (Table 1).

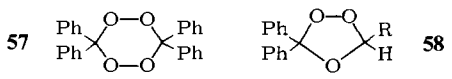
It is noteworthy that the dioxirane species **55** can be obtained from the photosensitized oxygenation of benzoylphenyldiazomethane, *via* **54** (Table 1)[87].



49

The photolysis of diphenyldiazomethane in presence of oxygen (Table 1) affords diphenyldioxirane **56**[88], which

can be isolated as the cyclic dimer **57**, or can be trapped by aldehydes to form the ozonides **58**[89].



57 **58**

Dioxirane **56** produced in this photolysis is capable of epoxidizing olefins[129], hydroxylating alkanes[90] and naphthalene[91], and of oxidizing sulfides to sulfoxides and ketones to esters[87].

The epoxidation of highly nucleophilic olefins such as 2,3-dimethyl-2-butene by 3,3'-dibromobenzoyl peroxide[92] has been interpreted by *Kwart* as being due to the formation of a reactive acyloxy-substituted dioxirane **59** (Table 1)[61].

The peroxy acid-like reactivity of the N, S, Se, and As peroxides depicted in Table 1 might also be attributed to the transient formation of reactive heterodioxiranes.

Epoxidation of olefins by molecular oxygen in presence of tetramethyl-2-tetrazene and $ZnCl_2$ probably occurs *via* formation of the dimethylamino peroxide/$ZnCl_2$ complex **60**, in which zinc chloride exerts an electron-acceptor effect on the nitrogen atom (Table 1)[93].

The reaction of H_2O_2 with *S,S*-dialkoxy-2,1λ^4-benzoxathiol **61** at −78 °C produces a reactive species **62** (Table 1) capable of oxidizing sulfides and of epoxidizing olefins[94]. A 1,2,3λ^4-dioxathiirane **63** of this type has been trapped as a transient intermediate in the singlet oxygen oxidation of diethyl sulfide[95].

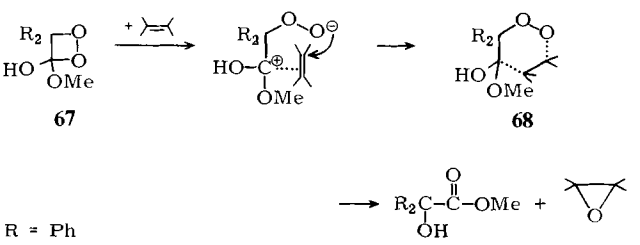
63

The same kind of reactive heterodioxirane may also arise in the rearrangement of peroxyselenic acids **64**[96,97] and peroxyarsonic acids **65** (Table 1)[98].

The involvement of reactive dioxirane intermediates in the ketone-catalyzed decomposition of potassium peroxomonosulfate, has been shown from ^{18}O-labeling experiments and kinetic studies[99].

Even weakly nucleophilic olefins are epoxidized under mild conditions in high stereoselectivity by dioxiranes of this type[99].

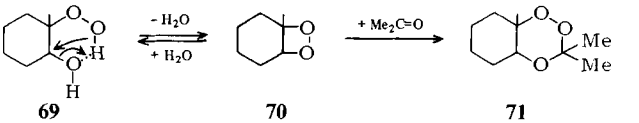
α-Hydroperoxy-ethers, -esters, (*e.g.* **66**) and -nitriles have recently been shown to epoxidize olefins[100]. These compounds rearrange to 1,2-dioxetanes (*e.g.* **67**) bearing electron-acceptor substituents on one carbon atom (Table 1). The epoxidation of olefins by the dioxetane could therefore occur by a 1,4-cycloaddition to form a six-membered peroxide intermediate **68**, which decomposes to epoxide and α-hydroxy ester.



67 **68**

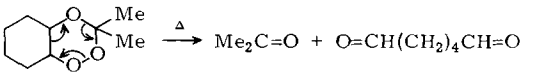
R = Ph

Such an insertion has been shown to occur in the reaction of the α-hydroxy hydroperoxide **69** with acetone, producing the ozonide **71**, probably *via* formation of the dioxetane **70**[83,101].



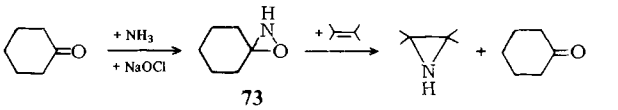
69 **70** **71**

Thermolysis of a similar perhydro-1,2,4-trioxane **72** at 160–180 °C produces acetone and adipaldehyde[102].



72

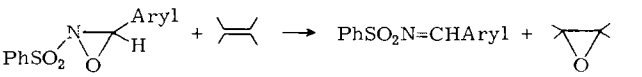
Finally, we should mention reactions of nucleophilic substrates with oxaziridines. The oxaziridine **73**, which is easily obtained from cyclohexanone, ammonia, and hypochlorite reacts with olefins to produce the corresponding aziridines[103].



73

This "epamination" of olefins by **73** has been shown to be very similar to epoxidation by peroxy acids.

Aryl(phenylsulfonyl)oxaziridines such as **74** have also recently been reported to cause asymmetric oxidation of sulfides to sulfoxides[104] as well as the epoxidation of olefins[130].



74

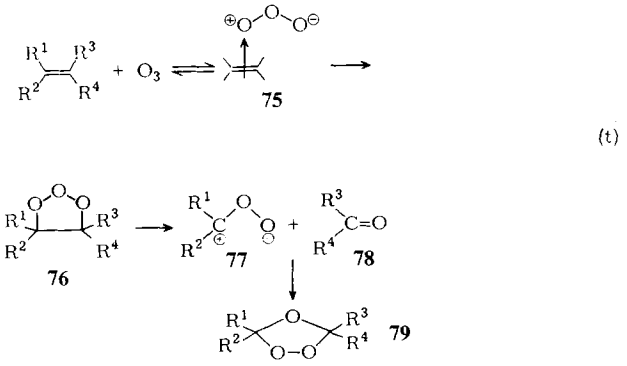
Hence, formation of dioxiranes (or 1,2-dioxetanes) as reactive intermediates appears to be a common denominator for most of the organic peroxide oxidizing agents. The various ways used for their preparation, the various oxygen sources from which they are formed ($^3O_2$, $^1O_2$, O_3, and H_2O_2), and the strong resemblance between these reagents and peroxy acids make possible a consistent rationalization of their reactivity in terms of intermediary dioxiranes.

3.3. Ozonization of Olefins

The reaction of ozone with olefins has been the subject of a great many investigations[105]. Here we will consider only selected aspects which are particularly relevant to oxidations by dioxirane reagents. The Criegee mechanism of ozonolysis, first proposed in 1949, is shown in (t)[63a].

3.3.1. Ozone-Olefin π-Complexes

Colored π-complexes such as **75** have been observed in the reaction of ozone with olefins such as 1-mesityl-1-phe-



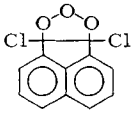
(t)

nylethylene at $-150\,^{\circ}C$[106], or in the reaction of ozone with arenes[107] or other olefins[108, 109] at low temperatures. The reversible formation of a π-complex between olefin and ozone as the rate-determining step was also suggested by *Cvetanovic et al.*[110] and *Fliszar et al.*[111] for interpreting the kinetic studies of ozonolysis of olefins; the analysis showed that electron-donor groups on the olefin have a rate-increasing effect, whereas electron-acceptor groups decrease the rate of ozonization. The relative rate constants for the ozonization of olefins are therefore similar to those previously shown for epoxidation by peroxy acids, MoO_5, and related dioxirane reagents.

3.3.2. Primary Ozonides (1,2,3-Trioxolanes)

Following the formation of the π-complex **75**, nucleophilic attack by the terminal oxygen atom occurs at the more substituted carbon of the olefin, producing the 1,2,3-trioxolane **76**. If the olefin has sterically very bulky groups at this site, as *e.g.* in 1-mesityl-1-phenylethylene[112] or adamantylideneadamantane[113], the π-complex **75** directly loses molecular oxygen and thus produces the epoxide.

The 1,2,3-trioxolane **80** has recently been isolated from the reaction of ozone with 1,2-dichloroacenaphthylene[114].



80

A crystalline compound obtained in the ozonization of *E*-2,2,5,5-tetramethyl-3-hexene ((*E*)-di-*tert*-butylethylene) at $-78\,^{\circ}C$, which can be reduced to racemic 2,2,5,5-tetramethyl-3,4-hexanediol (di-*tert*-butylethylene glycol), was previously also shown to be a 1,2,3-trioxolane[115].

3.3.3. Decomposition of Primary Ozonides to Carbonyl Compounds and "Carbonyl Oxide"

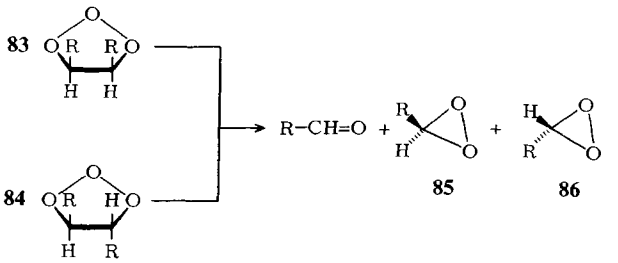
The trioxolane **76**, which results from the $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition of ozone to an olefin *via* a transition state with envelope conformation **39**[66], decomposes by a concerted 1,3-dipolar cycloreversion mechanism to give the carbonyl oxide **77** and the carbonyl compound **78**.

However, the original Criegee mechanism (t) does not satisfactorily account for some data concerning the ozonolysis of olefins: The geometry of the olefin considerably influences the stereochemical composition of the ozonides **79**, particularly for olefins having bulky groups attached to the double bond. For example, (*E*)-di-*tert*-butylethylene in non-polar solvents mainly produces the *trans*-ozonide, whereas the (*Z*)-isomer gives a 70:30 mixture of *cis*-:*trans*-ozonides[117, 118]. This led *Kuczowski* et al.[66] and *Bailey et al.*[105a, 116] to propose a stereochemical refinement to the Criegee scheme which takes into consideration that the decomposition of the primary trioxolane **76** produces unequal amounts of *anti*- (**81**) and *syn*-isomer (**82**) of the carbonyl oxide **77** (cf. isomerism in oximes), which in turn recombine with the carbonyl compound stereoselectively to yield *cis*- and *trans*-ozonides **79**[116].

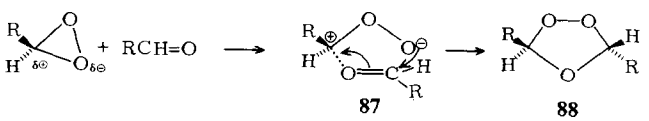
However, other observations cannot readily be incorporated into the Criegee scheme[119]. This applies particularly to solvent and stereochemical effects: the amount of ozonide produced from di-*tert*-butylethylene decreases in polar solvents[118], and the *cis*:*trans* ratio of the final ozonides depends on the solvent, olefin-concentration, and warming-up rate[120]. These results have been interpreted in terms of a nonconcerted addition of carbonyl oxide to the carbonyl compound[118b, 65a], whereas *Bailey et al.*[120] suggested an equilibration of the *syn*- and *anti*-forms of the carbonyl oxide. However, such an equilibration between **82** and **81** has recently been shown by theoretical considerations to be unlikely, since the barriers to rotation and inversion of **82** and **81** were found to be 31 and 41 kcal/mol, respectively[65c].

An alternative explanation on the basis of the rationale developed in this article could be made:

1) The decomposition of the *cis*- and *trans*-primary ozonides **83** and **84** occurs *via* a concerted 1,3-dipolar cycloreversion to give the carbonyl compound and unequal amounts of the two enantiomeric dioxiranes **85** and **86**, in which the C—O distances are different.



2) In the rate-determining step the carbonyl compound reacts with the dioxirane to form a charge-transfer π-complex **87**; this is followed by 1,3-dipolar cycloaddition to give the ozonide **88**.

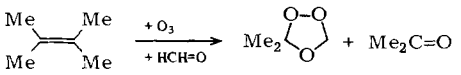


Theoretical investigations have shown dioxirane species to be the most stable form of the peroxymethylene com-

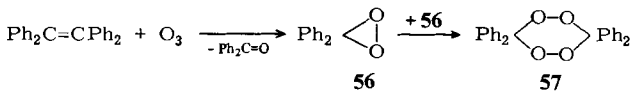
pounds resulting from the decomposition of primary ozonides[65], and they have been identified in the gas-phase ozonolysis of ethylene[64]. If the C—O distances are different, they can also exist in different enantiomeric forms. Since dioxiranes are isoelectronic with ozone, it is also expected that the carbonyl compound coordinates to the electron deficient carbon atom of the dioxirane ring. This coordination should be strongly inhibited by complexing agents which prevent ozonide formation, and should be strongly influenced by solvent effects and the bulkiness of the substituents attached both to the dioxirane ring and to the carbonyl compound. Note should be taken of the similarity between ozonide formation from dioxirane and carbonyl compound and the mechanism of both the Baeyer-Villiger oxidation [reaction (s)] of carbonyl compounds and the formation of stable metal-ozonides from peroxoplatinum complexes [reaction (e)].

3.3.4. Reactivity of Dioxiranes from the Ozonization of Olefins

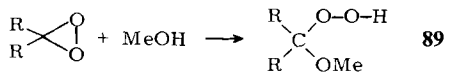
Dioxiranes can be trapped by "foreign" aldehydes, particularly when the ozonization of the olefin gives rise to the formation of ketones[105].



The ozonolysis of tetrasubstituted olefins produces dioxiranes, which can be isolated as cyclic dimers (*e.g.* **57**)[105, 121]; these are similar to the species obtained from the reaction of H_2O_2 with ketones[83].



When the ozonolysis of olefins is carried out in the presence of protic compounds (ROH, RCOOH, NH_3, HCN), hydroperoxides **89** are produced from the protonation of the dioxirane[105]. This reaction bears some similarity to the protonation of peroxo transition-metal complexes.

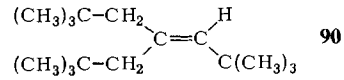


89

It would therefore be expected that dioxirane compounds produced by the ozonolysis of olefins, which resemble those in Table 1 obtained from various oxygen sources, should be able to epoxidize olefins and to cause the Baeyer-Villiger oxidation of carbonyl compounds to esters[61].

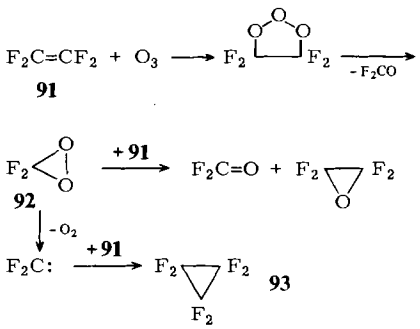
Of the many "anomalous" products of ozonolysis, epoxides and Baeyer-Villiger oxidation products should be mentioned as examples. Epoxide formation during ozonolysis of olefins occurs under two main circumstances:

1) When the olefin is sterically highly hindered, for example **90**[122], epoxide formation probably results from the direct decomposition of the olefin-ozone π complex **75** in which the nucleophilic attack by the negatively charged terminal oxygen atom is strongly inhibited [reaction (t)].



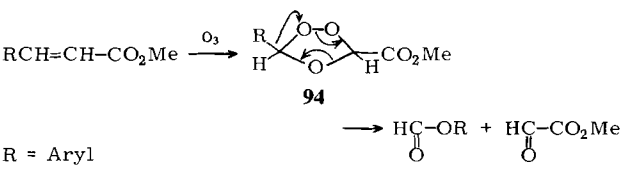
90

2) With electron deficient olefins[105], *i.e.* when ozonolysis produces dioxiranes having a strongly electrophilic carbon atom in the ring. A representative example is the ozonolysis of tetrafluoroethylene **91** yielding mainly $F_2C{=}O$ and epoxides[123], in which the difluorodioxirane **92** produced corresponds to the species **47a** obtained in the reaction of hexafluoroacetone with H_2O_2 (Table 1).

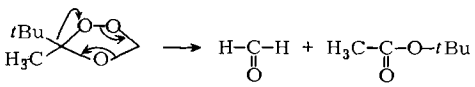


A small amount of **93** presumably results from the reaction of the carbene F_2C: (obtained from the decomposition of **92**) and tetrafluoroethylene **91**.

Baeyer-Villiger oxidation products have also been observed in the ozonolysis of cinnamic acid esters[124]. These products probably arise from the decomposition of the ozonide **94** (owing to the great migratory aptitude of the aryl substituents)[105].

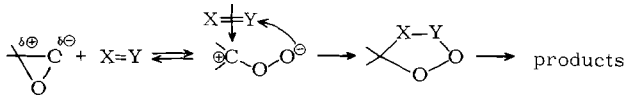


A decomposition reaction of this type has been shown to occur for the ozonide **95**[125].



4. Concluding Remarks

Oxygen transfer from organic peroxides to nucleophilic organic substrates can be described in terms of a two-step mechanism: Firstly, reversible formation of a charge-transfer complex between the nucleophilic substrate and the electrophilic carbon atom of the dioxirane ring in the rate-determining step, and secondly nucleophilic attack of the terminal oxygen atom at the "coordinated" substrate, forming a cyclic peroxide.



The formation of the charge-transfer complex is greatly accelerated as both the nucleophilicity of the substrate and the electrophilicity of the carbon atom of the dioxirane ring increase: it is strongly inhibited by complexing agents competing with the substrate. In the second step, nucleophilic attack occurs stereoselectively at the more substituted carbon atom of the substrate and is hindered by bulky substituents. The resulting cyclic peroxide is either stable (*e.g.* ozonides, X=Y ≙ C=O) or may decompose by 1,3-dipolar cycloreversion to produce the oxygenated substrate and the reduced peroxide reagent. This decomposition step, although not yet clearly elucidated, seems to be strongly dependent on the geometry of the cyclic intermediate (envelope conformation) and the nature of the substituents attached to the dioxirane and the substrate.

The structure and reactivity of the dioxiranes appear to be closely related to those of peroxo transition-metal complexes, which also form stable "metal-ozonides" (cf. **5**) with ketones and metallacycles (with group VIII metals) with electrophilic olefins (cf. **7**): their reactivity is also enhanced by the nucleophilicity of the substrate and by the electrophilicity of the metal, is inhibited by complexing agents, and is strongly dependent on the availability of vacant coordination sites at the metal. The decomposition of peroxometallacycles depends both on the substituents on the substrate and on the nature of the metal.

The reactivity of alkyl peroxide or hydroperoxide complexes with olefins differs from that of peroxo complexes: the second step is a *cis*-insertion instead of a 1,3-dipolar cycloaddition but the "pseudo"-dioxametallacycles decompose in the same way as the cyclic systems obtained from peroxo complexes, producing the same oxygenated products.

The aim of this article has been to provide a non-exhaustive approach to understanding selective oxygen-transfer reactions from inorganic and organic peroxides to organic substrates. We are aware of the fact that the joint treatment of two different fields may seem rather arbitrary and somewhat speculative, but we believe that both areas are sufficiently well developed to encourage communication between organic and inorganic chemists.

We are also aware that this article is incomplete, since it does not treat the relevant hydroxylation reactions which are common to organic[90, 127] and inorganic reagents[126]. Although a considerable amount of evidence suggests a unified view of oxygen-transfer reactions from peroxides, the most compelling proof will be hopefully given by the isolation of well-characterized, reactive organic dioxiranes.

In the inorganic area, much still has to be carried out to develop tailor-made syntheses for the selective oxidation of organic substrates. The recent use of $Ti(OiPr)_4$-diethyltartrate for the asymmetric epoxidation of allylic alcohols by *t*-BuOOH[131] is an example of the usefulness and superiority of peroxo transition-metal reagents in effecting a variety of selective transformations.

After this manuscript had been submitted for publication, several relevant contributions in this area appeared. In transition-metal oxidation reaction chemistry, these involve an important and useful book by *Sheldon* and *Kochi*[132], and articles on: titanium-catalyzed asymmetric epoxidation of allylic alcohols by *t*-BuOOH[131]; epoxidation of olefins by O_2+H_2[133], O_2+NaBH_4[134], PhIO[135], and NaOCl[136] catalyzed by manganese porphyrins; catalytic epoxidation of olefins by alkyl hydroperoxides[137]; ketonization of olefins catalyzed by group VIII transition-metal complexes[138], by Pd—NO_2 complexes (with the characterization of the five-membered metallocyclic intermediate)[139], by Pt—OO*t*Bu species[140], and by O_2+H_2 in the presence of iridium complexes[141, 145].

Oxygen-transfer reactions from organic peroxide reagents have also been the focus of recent investigations. Carbonyl oxides generated from the photolysis of diazo compounds have been shown to act as effective nucleophilic oxygen-atom transfer reagents[142], and decarboxylating agents of α-keto carboxylic acids[143]. It has also been shown that in the three step Criegee mechanism [reaction (t)], the carbonyl oxide determines the stereochemistry for lower olefins and the primary ozonide that for higher olefins[144].

I wish to thank my coworkers cited in references who have largely contributed to the work carried out in our laboratory. I am grateful to Professor Sir D. H. R. Barton, Professor H. J. Kagan, and Professor Harold Kwart for their interest in this work, and their remarks and criticism.

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[145] *Note added in proof:* We have recently found that well-characterized covalent vanadium(v) peroxo complexes act as effective versatile oxidants for a) epoxidation of olefins in a non-stereoselective fashion (*e.g. cis*-olefins give *cis* + *trans* epoxide mixture), b) hydroxylation or aromatics (*e.g.* benzene to phenol) and c) hydroxylation of alkanes with a significant amount of epimerization at the functionalized carbon atom (*e.g. cis*-decalin gives a mixture of *cis* + *trans* 9-decalol). This behavior, which is very different from that of Mo peroxo complexes, was attributed to the reactive biradical $V^{IV}OO^{\cdot}$ species (generated from the homolytic cleavage of the V(v) peroxo group) which can add to olefins and aromatics and abstract hydrogen atoms from alkanes. It is noteworthy that some dioxirane species such as **56** (Table 1) exhibit a similar behavior and may therefore react as their homolytically dissociated $R_2C^{\cdot}-OO^{\cdot}$ form. This reactivity is reminiscent of that of enzymic cytochrome P_{450} monooxygenases. H. Mimoun, L. Saussine, E. Daire, M. Postel, J. Fischer, R. Weiss, *J. Am. Chem. Soc.,* (submitted for publication).

Prostacyclin and Synthetic Analogues

By Wilhelm Bartmann* and Gerhard Beck

Dedicated to Professor K. Weissermel on the occasion of his 60th birthday

The prostanoids continue to attract a great deal of attention, particularly in the pharmacological sector. Many of the numerous biological studies on prostaglandins deal with their cardiovascular effects. The pronounced antihypertensive and platelet aggregation-inhibiting properties of prostacyclin (PGI_2) resulted in world-wide efforts to synthesize acid-stable analogues of the natural product. Whereas refined analytical procedures disproved the hypothesis that PGI_2 is a circulating hormone, exploratory human trials with PGI_2 confirmed the pharmacological findings obtained from animal experiments. Clinical studies of PGI_2 analogues have been started. *In vitro* studies on isolated vessels revealed that potent cardiovascular drugs stimulate prostacyclin synthesis; however, it has not as yet been possible to demonstrate whether these effects are also of therapeutic significance. A survey of the PGI_2 analogues synthesized so far is presented, and, with the aid of a few examples, the problems encountered during their synthesis are outlined; structure-activity relationships are also discussed.

1. Introduction

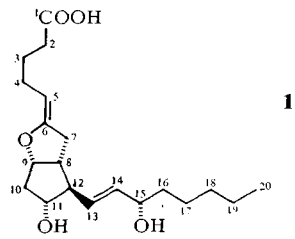
Since publication of the first reports on prostaglandins by *Goldblatt*[1,2] and *von Euler*[3] in 1933 and 1934, interest in this field, which remained dormant for a long time, has increased dramatically, particularly over the past 20 years. Numerous review articles[4–7] and monographs[8] on various aspects of prostaglandin research have now been published. The title of the last paper on this subject in Angewandte Chemie in 1978[4] "Synthesis and Biological Properties of Prostaglandin Endoperoxides, Thromboxanes and Prostacyclins" revealed that further biologically highly active members of the family of prostaglandins had been discovered.

Only one year later, at the 4th International Prostaglandin Conference in Washington[9], the introductory lecture by *Samuelsson*[10] no longer dealt with prostanoids, but rather with leucotrienes, thus opening a new field of study concerning the metabolism of polyunsaturated fatty acids in the mammalian organism.

The research results of the last 50 years are summarized in Schemes 1 and 2. Briefly, they demonstrate that unsaturated fatty acids of the arachidonic acid type are oxidized by two enzyme systems—cyclooxogenase and lipoxygenase—to oxygenated fatty acid derivatives. These natural products may be characterized biologically by their effect on smooth muscle—they contract or dilate smooth muscle organs. The two schemes also demonstrate that the article by *Nicolaou et al.*[7] may be considered to be the last attempt to provide the chemist not concerned with unsaturated fatty acids an overview of the entire field of research.

Prophylactic treatment of angiopathic patients with unsaturated fatty acids has been indicated for many years. The fact that we are now able to demonstrate the constitution and biological effect of the physiological oxidation products of unsaturated fatty acids using refined methods makes research in this field attractive. This is particularly true, for, after cancer, angiopathies have become the most important health risk for the population of the western world.

Since it has become very difficult to give a survey of the whole field of physiological metabolites of unsaturated fatty acids, in the present paper we shall concentrate on prostacyclin (PGI_2)[12] **1** and its synthetic analogues. Ever



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since the time of its discovery prostacyclin has attracted a great deal of attention from the therapeutic viewpoint because of its blood pressure-lowering and platelet aggregation-inhibiting effects[13]. For the medicinal chemist it is still the most important representative of the prostanoids and—in a broader sense—of the physiological metabolites of unsaturated fatty acids.

2. Prostacyclin and its Biological Properties

One may differentiate the biological effects of prostacyclin as follows:

- Pharmacological effects induced by the administration of prostacyclin in animal and human studies.
- Physiological significance of prostacyclin PGI_2 **1** as a local hormone and its interaction with its physiological "opponent" thromboxane (Scheme 1).

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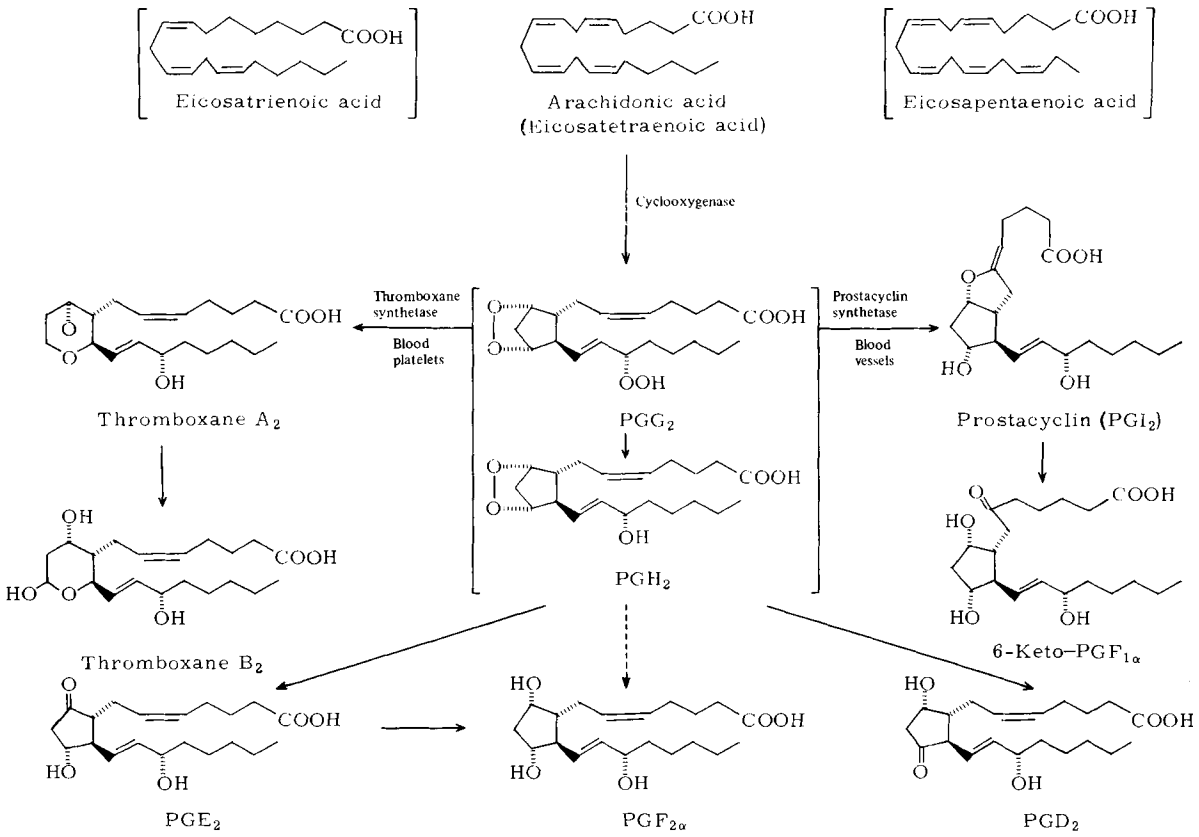
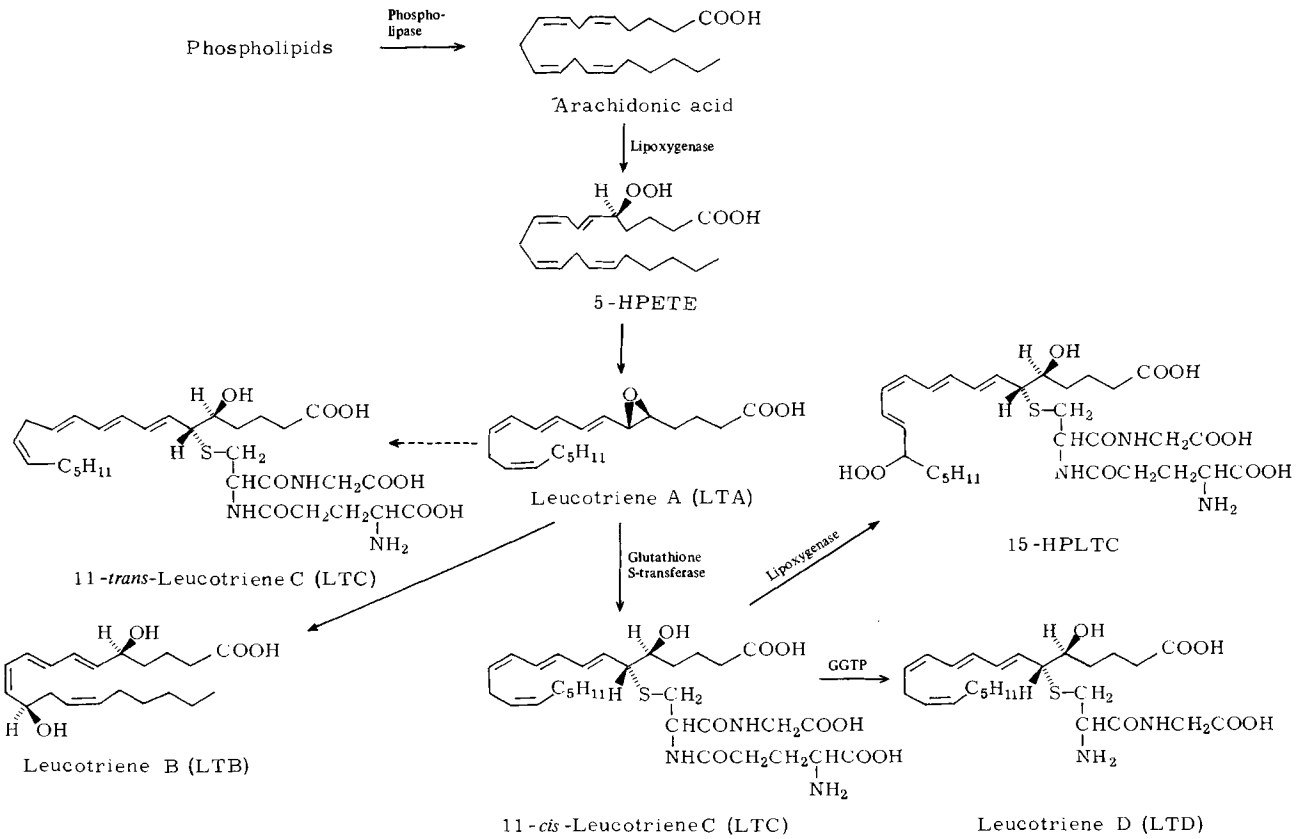


Scheme 1. Synthesis of prostaglandins and thromboxanes from arachidonic acid. The eicosatrienoic and eicosapentaenoic acids in brackets in the top row lead to compounds with one double bond and two double bonds, respectively.



Scheme 2. Formation and transformation of the leucotrienes; GGTP = γ-glutamyltranspeptidase; 5-HPETE = 5-hydroperoxyeicosatetraenoic acid; 15-HPLTC = 15-hydroperoxyleucotriene C.

- Change in prostacyclin levels under pathophysiological conditions.

2.1. Pharmacological Effects

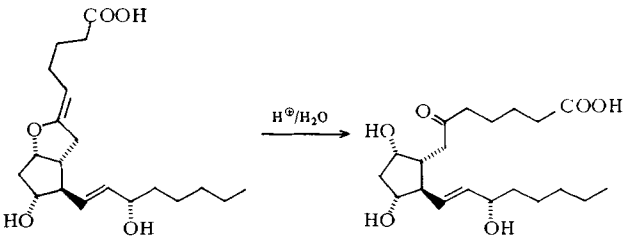
The platelet aggregating and vasodilating properties of prostacyclin observed in animal experiments were more rapidly confirmed in human trials than in the case of the "classic" prostaglandins. *Gryglewski* and *Szczeklik et al.*[14] reported in an article entitled, "Circulatory and Anti-Platelet Effects of Intravenous Prostacyclin in Healthy Man", that intravenous infusion of 2—50 ng/kg/min induced vasodilation in the skin of the head, the neck, and the palms. Whereas the diastolic blood pressure was lowered, the systolic pressure remained almost unchanged, and the heart rate was increased. In particular, platelet aggregation was suppressed. A further study at the Copernicus Academy for Medicine in Krakow[15] revealed that inhalation or infusion of prostacyclin in the above mentioned doses had no marked influence on the respiratory tract. This finding has since been confirmed in a review article on animal and human studies[16].

In 1981, a report was published on the side-effects observed during infusion of prostacyclin sodium in 27 volunteers under the title, "Intravenous Infusion of Prostacyclin Sodium in Man"[17]. This study showed that healthy volunteers could tolerate short-term infusion of prostacyclin sodium at rates of up to 10 ng/kg/min; higher doses cause headache, feelings of anxiety, nausea, and vomiting. The side-effects exhibited a linear relationship to the infusion rate. The maximum tolerated dose was a 24-hour infusion of 4 ng/kg/min. ADP-induced platelet aggregation was inhibited in a dose-dependent manner. The platelets showed increased levels of cyclic AMP. The authors concluded that the therapeutic index of the natural product is relatively small. Prostacyclin may, however, be administered safely in human trials if caution is applied. *O'Grady et al.*[18a] obtained analogous results. They established that the increase in stroke incidence, the reduction in diastolic blood pressure, the increase in heart rate, and increase in peripheral temperature are consistent with the vasodilating properties of prostacyclin.

Human trials thus confirm the hypothesis derived from animal studies that prostacyclin is a highly potent natural product possessing desirable cardiovascular activity.

Nevertheless, prostacyclin does not yet have the therapeutic index required to be administered without cardiovascular side-effects as, for example, in the case of pathologically increased platelet aggregation. The disadvantage of the relatively low therapeutic index is further exacerbated by the poor chemical stability of prostacyclin at physiological pH[18b]. Hydrolysis mainly leads to 6-oxo-$PGF_{1\alpha}$ **2**.

The activity of prostacyclin, in contrast to that of the E- and F-prostaglandins, seems to be more organ-specific, at least according to our present state of knowledge. *O'Grady et al.* investigated the effect of prostacyclin on renal function in man and found that it would seem to have no major effect on water and electrolyte excretion[19]. Whereas the effect of administered PGI_2 on the cardiovascular system



1 **2**

and platelet aggregation in man has been established, various other biological activities of prostacyclin could be investigated pharmacologically only in animal experiments. The finding that intravenous infusion of PGI_2 in anesthetized rats and conscious dogs induces a more pronounced antisecretory effect on the gastric mucosa than the infusion of PGE_2[20] (Scheme 1) may be of therapeutic interest.

The use of prostacyclin in humans seems to be promising for two instances, but further clinical evaluation is needed. In the extracorporeal circulation of blood, as is necessary in the case of artificial kidneys, the infusion of prostacyclin is designed to save heparin and to maintain normal platelet function. Moreover, prostacyclin is intended to avoid life-threatening hemorrhages in cardiopulmonary bypass operations where the coagulation time is affected by a reduction in the number of circulating platelets[21].

2.2. Physiological Properties

Whereas the pharmacological effects of prostacyclin in animal and human studies are reproducible, the question of the physiological significance of the natural product has not yet been sufficiently clarified.

There are several reasons for this: Reliable but difficult analytical methods for the detection of prostacyclin in body fluids have been developed only very recently (cf. Section 2.3), and, there is a great variety of interactions between unsaturated fatty acids in general, prostaglandins and prostacyclin in particular, and other biochemical control systems.

Even reducing the question to "Prostaglandins and the Cardiovascular System" (*i.e.* the subject of a symposium now available in book form[22]) has not solved the problems. Nor can a complete answer be provided by further limitation to the question of which prostaglandin regulates the release of renin[23] (*i.e.* a proteolytic enzyme of the kidney influencing the synthesis of vasopressor peptides).

The physiological importance of prostacyclin and its antagonist thromboxane (TXA_2) is a subject of controversy. According to *Vane et al.*[24] prostacyclin is a "circulating hormone", whereas *Christ-Hazelhof* and *Nugteren* state in a recently published article[25] that prostacyclin is *not* a "circulating hormone". *Gryglewski et al.*[26] are of the opinion that the lungs *in vivo* secrete prostacyclin into the cardiovascular system, which, as a circulating hormone, is then responsible for homeostasis, whereas thromboxane (TXA_2) is able to repair lesions in the vascular musculature by the induction of platelet aggregation under physiologi-

cal conditions, but under pathophysiological conditions contributes to the development of arteriosclerosis. This concept was taken up as a working hypothesis by *Vane* and *Moncada* in 1979 to develop new methods for the prevention and treatment of vascular diseases[27]. It cannot be conceded that prostacyclin continually circulates in an organism and is necessary for the maintenance of normal blood pressure but it is correct, that prostacyclin and thromboxane have a "repair function". The contradictory opinions are due to different results which were obtained from prostacyclin level determinations under physiological and pathophysiological conditions.

2.3. Analytical Procedures

The prostaglandins were discovered in biological experiments, and, using their pharmacological activity as a means of detection, they could be isolated and purified in crystalline form[4]. Initially, the biological experiment was also the only practicable analytical method in the search for unstable metabolites of arachidonic acid, such as the prostaglandin endoperoxides. *Ferreira* and *Vane*[28] combined individual biological experiments to create the so-called "superfusion bioassay technique" and have since developed it further. In combination with the platelet aggregometer, the superfusion technique led to the discovery of prostacyclin by *Moncada et al.*[13]. In his final remarks at the Symposium, "Clinical Pharmacology of Prostacyclin", *Dollery*[29] explained the high values obtained from the superfusion technique in terms of the possibility that prostacyclin might be formed from leukocytes during isolation.

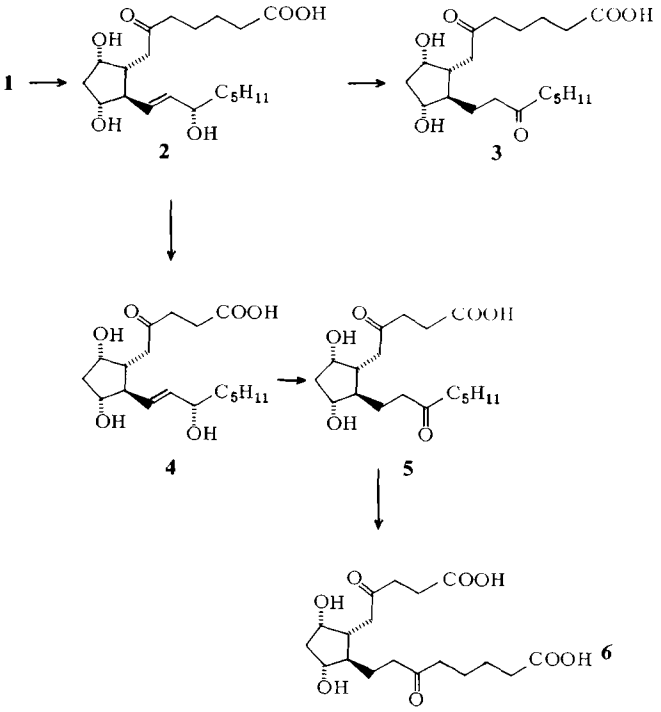
It is known that prostacyclin is, *inter alia*, hydrolyzed to 6-oxo-$PGF_{1\alpha}$ **2** at pH 7.2; therefore, prostacyclin determinations which are based on the measurement of this metabolite possibly yield values that are too high, for **2** has a longer half-life than prostacyclin itself and therefore accumulates[29].

The radioimmunoassay of **2** encounters similar difficulties to those observed during analysis of the classic prostaglandins because of possible cross-reactions with other prostaglandins and their metabolites.

A reliable determination of the prostacyclin level under physiological conditions can therefore presently only be obtained by means of the relatively difficult gas chromatography-mass spectrometry (GC-MS) technique or by gas chromatography combined with electron capture detection (GC-EC) after appropriate derivatization of the metabolite **2**. *Christ-Hazelhof* and *Nugteren*[25] concluded from GC measurements that neither human plasma nor whole blood contains more than 20 pG prostacyclin per mL. *Oates et al.* obtained similar results when determining the concentration of prostacyclin metabolites in urine[30].

In contrast to this, *Hensby*[31] reported markedly higher values: 130 pg/mL in healthy persons and 98 pg/mL in diabetics when he determined the concentration of **2** in plasma by means of quantitative GC-MS. For this reason, the presently most reliable method for measuring normal prostacyclin levels seems to be the determination of prostaglandin metabolites in the urine, as elaborated by *Frölich et al.*[32]. Using ^3H- and ^2H-labeled prostacyclin as well as ^3H-labeled 6-oxo-$PGF_{1\alpha}$, *Frölich et al.* identified dinor-6-oxo-prostaglandin-$F_{1\alpha}$ as the main renal metabolite of prostacyclin and 6-oxo-$PGF_{1\alpha}$ in man[33].

The metabolites of prostacyclin and 6-oxo-$PGF_{1\alpha}$ identified so far in man are summarized in Scheme 3 (after *Frölich et al.*)[34].



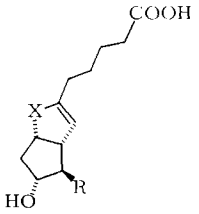
Scheme 3. Renal metabolization of prostacyclin (PGI_2) **1** and 6-oxo-$PGF_{1\alpha}$ **2** in man. **3**: 6,15-dioxo-13,14-dihydro-$PGF_{1\alpha}$; **4**: dinor-4-oxo-7,9,13-trihydroxyprosta-11-enoic acid; **5**: dinor-4,13-dioxo-7,9-dihydroxyprostanoic acid; **6**: dinor-4,13-dioxo-7,9-dihydroxyprostan-1,18-dicarboxylic acid.

2.4. Prostacyclin Biosynthesis under Pathophysiological Conditions

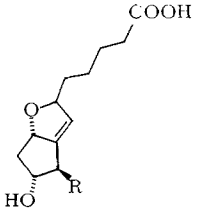
Disorders in prostacyclin biosynthesis are observed in arteriosclerosis[35], diabetes[36], and uremia[37]. In particular, numerous studies have established a connection between arteriosclerosis and a change in prostacyclin and/or thromboxane levels. This topic is dealt with in an informative article by *Szczeklik* entitled "Serum Lipoproteins, Lipid Peroxides, and Prostacyclin Biosynthesis in Patients with Coronary Heart Disease[38]. The statements regarding a change in prostacyclin levels under pathophysiological conditions need to be confirmed however, by reason of the above mentioned analytical problems.

3. Synthesis of Prostacyclin Analogues

Numerous hypotheses have been formulated about the biological significance and the therapeutic potential of prostacyclin[39,40]. Thus, *Moncada* and *Vane* have repeatedly postulated: "So far, prostacyclin is the most potent and comprehensive inhibitor of all forms of aggregation. This fact, together with the endogenous nature of prostacyclin, clearly suggests that the future of antithrom-



7a, X = O
7b, X = CH_2
7c, X = S



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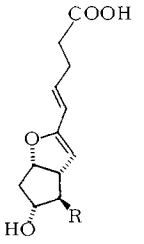

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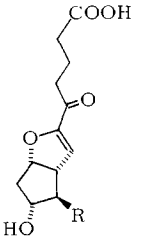

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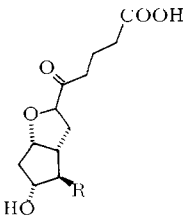

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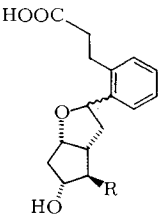

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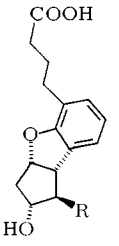
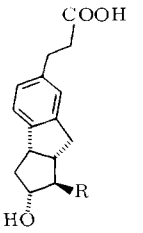
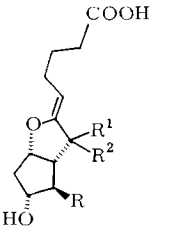


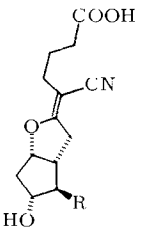
13a



13b



14a, R^1, R^2 = O
14b, R^1 = H, R^2 = OH



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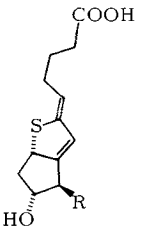

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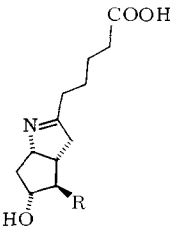

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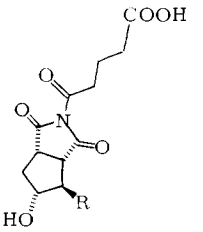

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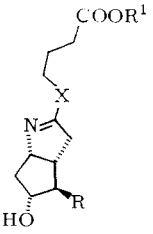
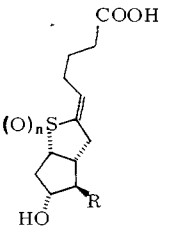
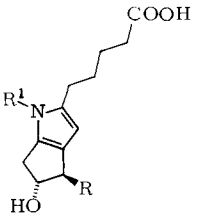


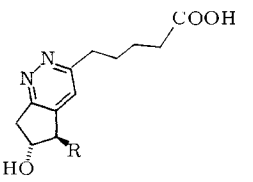
19a, X = O, R^1 = CH_3
19b, X = S, R^1 = CH_3
19c, X = NH, R^1 = H



20, n = 0,1,2



21a, R^1 = H
21b, R^1 = C_6H_5



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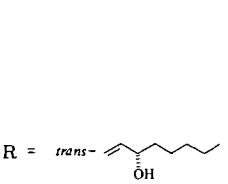
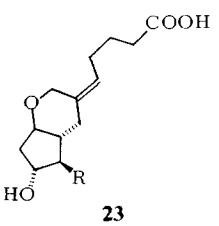


R = *trans*-



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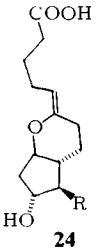


24

Scheme 4. Prostacyclin analogues. For further synthetic analogues see Scheme 10.

botic therapy for cardiovascular disease, including myocardial infarction, deep vein thrombosis, *etc.*, lies in the development of compounds with a prostacyclin type of action which are long acting, orally active and probably free from the cardiovascular effects of prostacyclin".

Owing to the pharmacological potential of prostacyclin, two principal possibilities for the future synthetic work of the medicinal chemist are conceivable: use of stable synthetic prostacyclin analogues (cf. Sections 3.1—3.4) or use of any cardiovascular compound which induces the same biochemical signals as prostacyclin (see Section 5). To our knowledge 24 prostacyclin analogues (Scheme 4) of different molecular structure were synthesized by various research groups between 1977 and March 1982.

3.1. Prostacyclin Analogues in which the Hydrolyzeable Enol Ether Double-bond is Stabilized

The prostacyclin isomer **7a**, in which the double bond has been shifted from the 5-*exo*- to the 6-*endo*-position, was synthesized by *M. Hayashi et al.*[41] and *Johnson et al.*[42] in 1978. The corresponding analogues with $X=CH_2$[43], **7b**, and $X=S$[44], **7c**, have also been synthesized recently by *Ikegami et al.*. **8**, a further double-bond isomer of prostacyclin, was synthesized by *Sih* and *Graber*[45] in 1978. *Pace-Asiak* and *Wolfe*[46] claimed to have isolated a substance with this structure in 1981. However, according to *Sih* and *Huang*[47] this natural product probably has another structure. *Ohno et al.*[48] also synthesized derivatives in which the double bond in the ring is shifted. **9**[48] contains in addition a conjugated double bond, in the 4-position, and **10**[49] an oxo-group in the 5-position. A hydrogenated analogue of **10**, the tetrahydrofuran derivative **11**, was prepared at about the same time by *Ayer et al.*[50].

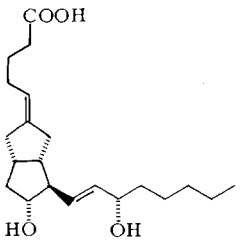
Sih et al.[51] applied the results of earlier studies and synthesized the phenyl derivatives **12**. Whereas the configuration at C-6 in **12** has not yet been clarified, the *cis*-configuration at the double-bond of the benzene ring linked to the tetrahydrofuran system by condensation has been established in the case of the analogue **13a** synthesized by *Ohno et al.*[52]. *Hayashi et al.*[53] reported in 1980 on the synthesis of **13b** which contains an annelated benzene ring and in which the oxygen atom in the 9-position is replaced by a CH_2-group. *Tömosközi et al.*[54] and *Bannai et al.*[55] have synthesized a 7-oxo- **14a** and a 7-hydroxy-derivative **14b**, respectively. In the analogue **15** prepared by *Vorbrüggen et al.*[56] the improved stability towards hydrolysis is achieved by a 5-cyano group.

3.2. Prostacyclin Analogues in which either O-9 is Replaced by Another Heteroatom or in which Additional Heteroatoms are Present

Aside from the already well-known thia-analogue **16**[57-60] and the aza-analogue **17**, in 1979 *Hayashi et al.*[62] were able to synthesize the trioxo-compound **18**; *Bartmann et al.*[63] reported compounds **19a—19c**, having the 5-membered ring and the 5-membered carbon chain in common with prostacyclin, and in addition carrying heteroatoms in various positions. The heteroprostacyclin analogues **20**, in which the sulfur is in a higher state of oxidation were prepared by *Nicolaou et al.*[64,65], *Wakatsuka et al.*[66], and by *Ikegami et al.*[67]. In the heteroanalogues **21a**[68a] and **21b**[68b], the tetrahydrofuran ring of prostacyclin has been replaced by a pyrrole ring. All these analogues have in common that C8 of the prostanoid structure is separated from the carboxy group by six atoms. This holds true also for the pyridazine-derivative **22** described by *Nicolaou*[69], as well as for **23**[70] and its isomer **24**[71,72] in which the tetrahydrofuran ring is expanded to a tetrahydropyran ring.

3.3. Carbacyclin

Among the prostacyclin analogues described since 1977, carbacyclin **25** deserves special attention. Initial results obtained in clinical trials after intravenous and oral administration of carbacyclin to man were reported by *Karim et al.*[73] in 1981. In these studies, intravenously infused carbacyclin (20 to 80 ng/kg/min) significantly inhibited the *ex vivo* ADP-induced platelet aggregation and, in contrast to PGI_2[74], was tolerated without any side-effects. According to initial results, oral doses were effective, but less well tolerated.

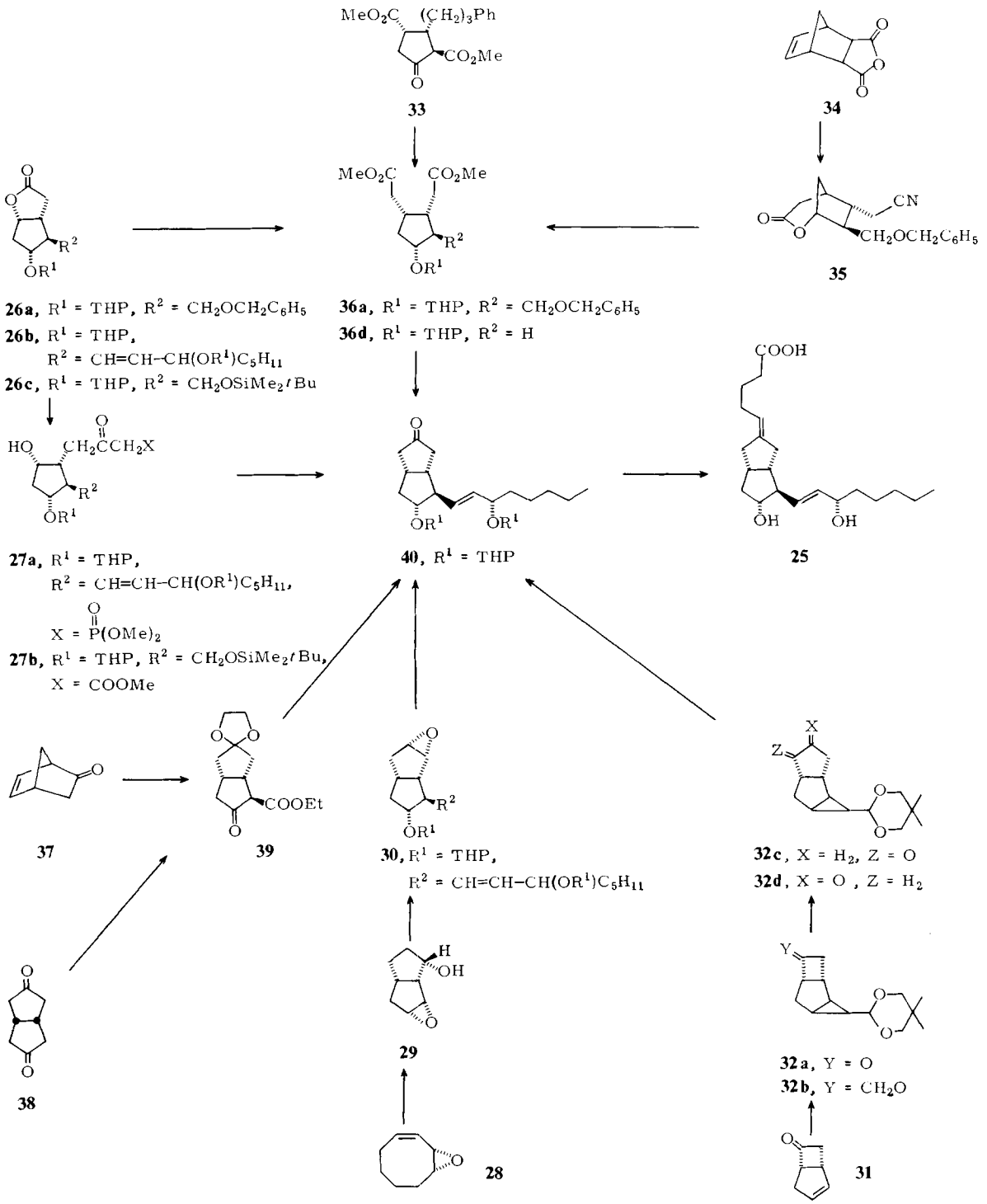


25

The total synthesis of carbacyclin was described almost simultaneously by several research groups[75,79,81,90]. They are in part a repetition of "classic" prostaglandin syntheses (Scheme 5). A detailed discussion of the multi-step synthetic routes is therefore considered unnecessary, and only important educts and relevant synthetic steps will be discussed.

The starting material in the total synthesis of carbacyclin and related isomers published by *Morton* and *Brokaw*[75] is the cyclobutanone derivative **32a** which was known from earlier studies. The product is transformed with dimethylsulfonium methanide into the isomeric spiroepoxides **32b**, using the method described by *Corey*[76] *et al.*. A major step in this carbacyclin synthesis is then a regioselective ring enlargement of this spiro compound[77], whereby a mixture of the isomeric cyclopentanones **32a** and **32d** is formed in a ratio of 1:9. The main product **32d** required for further synthesis may be crystallized from the crude reaction mixture in 60% yield. The subsequent reaction steps, *i.e.* formation of the ω-side chain and stereospecific hydroxylation at C-15, afford **40** and follow the known synthetic route of *Kelly et al.*[78].

The final synthesis step is a Wittig reaction with the *cis*-bicyclo[3.3.0]octan-3-one synthon **40**. This reaction has to be carried out with an excess of Wittig reagent, because the ketone shows a tendency towards enolization.



Scheme 5. Total synthesis of carbacyclin **25**. THP = tetrahydropyranyl.

The carbacyclin synthesis published slightly earlier by *Kojima* and *Sokai*[79] likewise employed the Wittig condensation with **40** as the final synthetic step; as in the case of the synthesis of *Kelly et al.*, the desired *cis*-isomer **25** is formed in a 1 : 1 ratio with the corresponding *trans* isomer. The stereospecific production of the *cis-trans* diester **33** and its transformation into **36d** by *Kojima* and *Sakai* is based on earlier work published by the same authors[80].

Gandolfi[81], *Nicolaou et al.*[90], and *Shibasaki et al.*[83] used *cis*-bicyclo[3.3.0]octan-3,7-dione **38** as starting material in their carbacyclin syntheses. An additional important intermediate in all three syntheses is the monoketal **39**. In order to circumvent the partial hydrolysis necessary for production of **39** from the diketal **38**, *Gandolfi*[82] described in 1980 a modified procedure starting from 5-norbornen-2-one **37**.

The ester group in **39** can be transformed into the ω-side chain by conventional methods and results in **40**, which is further converted under standard Wittig conditions into **25**.

In another synthesis of the carbacyclin **25**, *Shibasaki et al.* used 1,3-cyclooctadiene[83] as adduct; after epoxidation to **28**, the epoxide **30** is obtained *via* the endoepoxide **29**. Oxidative ring opening of epoxide **30** with Collins' reagent furnishes a mixture of the desired *cis*-bicyclo[3.3.0]octan-3-one derivative **40** and the isomeric *cis*-bicyclo[3.3.0]octan-2-one derivative in the ratio 1:2.

Two further total syntheses of the carbacyclin **25**[84,85], which also start from 1,3-cyclooctadiene, differ only in the transformation of the adduct into the *cis*-bicyclo[3.3.0]octan-3-one synthon **40**.

Sugie et al.[86] carried out a multi-step total synthesis based on previous studies with prostaglandins[87a]. This synthesis begins with the conversion of the 5-norbornene-2,3-dicarboxylic acid anhydride **34** into the lactone **35**. Hydrolysis of the lactone and the nitrile group in **35** with potassium hydroxide, and subsequent esterification of the resulting carboxylic acid with diazomethane affords diester **36a** which is then transformed in a Dieckmann condensation with subsequent decarboxylation and introduction of the ω-side chain into the carbacyclin precursor **40**.

Three further synthetic routes to carbacyclin **25** start from the derivatives **26a**—**26c** of the commercially available and optically active "Corey lactone". The key synthon **40** of all carbacyclin syntheses is then obtained by formal replacement of the oxygen atom in lactone by a methylene group.

In the first published synthesis according to the above principle[87b], sodium hydroxide is used to open lactone **26a**. The subsequent homologization of the oxoester obtained after oxidation with chromyl chloride leads to the tetrasubstituted cyclopentane derivative **36a**. This is then cyclicized by a Dieckmann condensation and transformed into **40** by subsequent introduction of the ω-side chain by known methods. *Aristoff*[88] opened **26b**, with dimethyl lithiomethylphosphonate to give **27b**, from which **40** is finally obtained *via* a substituted *cis*-bicyclo[3.3.0]octenone. In the recently published synthesis by *Skuballa* and *Vorbrüggen*[89], ring opening of **26c** is achieved with lithiated ethyl acetate; further transformation of the intermediate product **27b** leads *via* an intramolecular Michael addition to **40**.

A critical assessment of all synthetic routes must remain speculative, since each research group has used its own experiences which had been gained with prostaglandin chemistry over several years. Although the route from ketone **31** *via* the intermediate **40** to carbacyclin **25** described by *Kelly* and *van Rheenen*[78] may be tedious, it seems, due to synthetic "know-how", to be as practicable as the, apparently, more elegant syntheses starting from structures **37** and **38**[81-83,90].

The outstanding importance of *Corey*'s prostaglandin syntheses remains undisputed and the strategies developed at the end of the sixties could be applied to problems which did not appear until the advent of prostacyclin chemistry in the late seventies. For this reason, the synthetic route from **26b** *via* **27b** and **40** to **25** deserves special attention[88], all the more so because a precursor of **26b** may be obtained in optically active form from a commercially available intermediate.

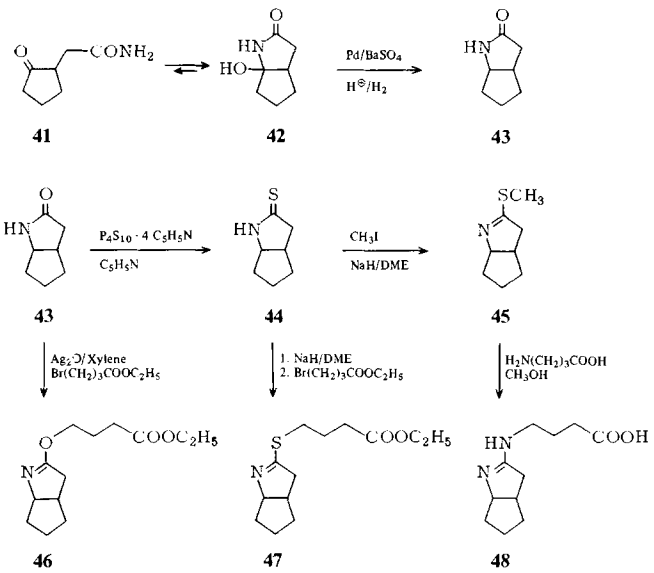
The synthetic routes summarized in Scheme 5 demonstrate quite clearly, even to the non-expert, that prostaglandin chemistry has begun, at least partially, to match steroid chemistry and has become attractive not only from the commercial standpoint, but also for experimental studies in the field of carbocyclic natural product chemistry.

3.4. Heteroiminoprostacyclins

Heteroanalogues of prostacyclin, in which the oxygen atom is replaced by a nitrogen atom or sulfur atom, have less favorable biological properties than prostacyclin[90,91].

In order to replace the enol-ether moiety by an isoelectronic group, the β-heteroiminoprostacyclins **19a**—**19c** were synthesized.

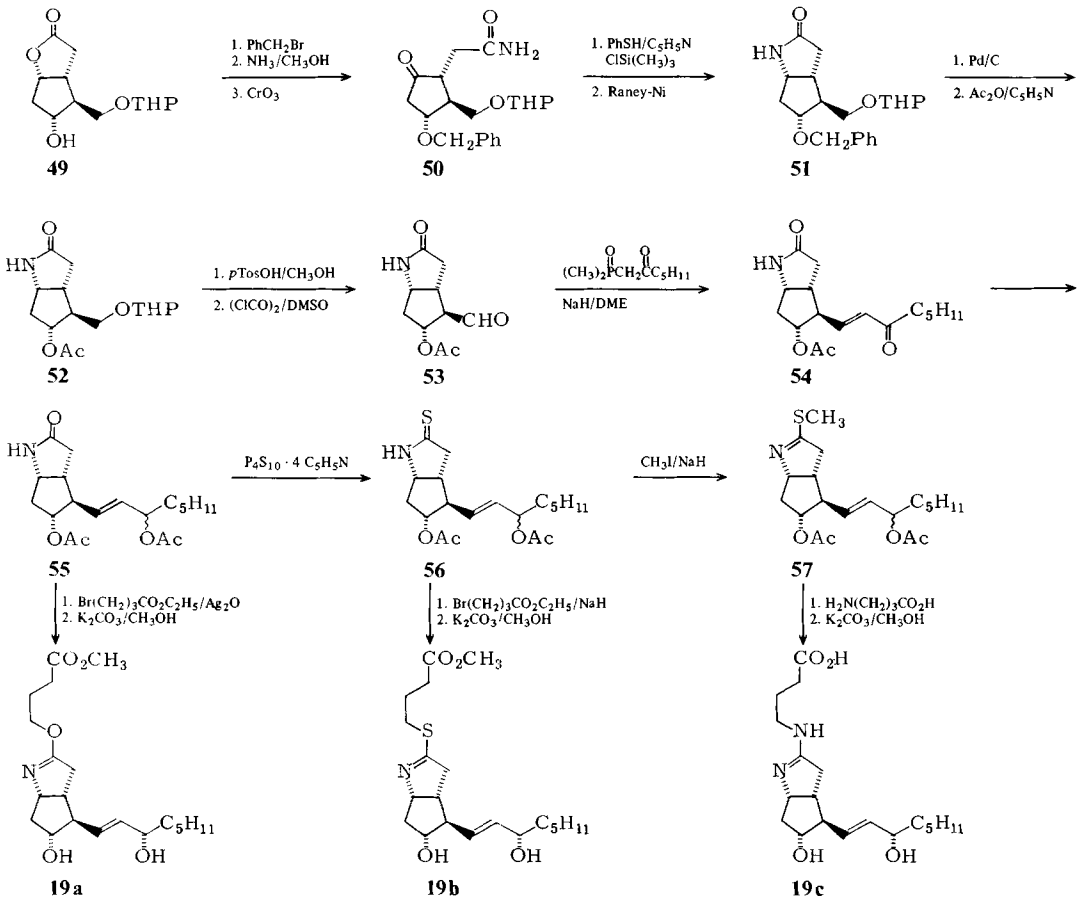
In addition, by simplification of the structure it was possible to investigate to what extent the electron-rich double bond of the enol ether was responsible for the biological properties of prostacyclin. They key reaction for obtaining such heteroiminoprostacyclins consists in tautomerizing 2-oxocyclopentylacetic acid amide **41** to the corresponding lactamol **42** (Scheme 6).



Scheme 6. DME = dimethoxyethane.

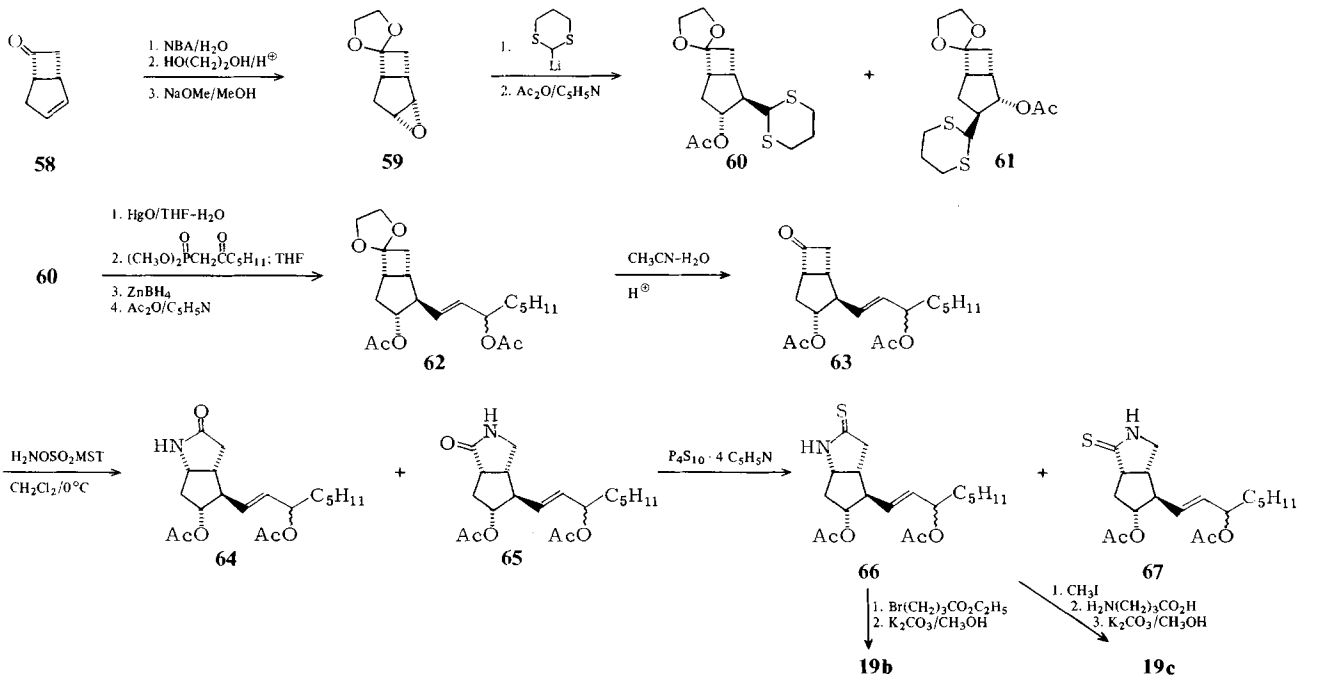
The OH-group can be eliminated from lactamol **42** by reduction, and the lactam **43** thus obtained converted into the corresponding thiolactam **44** by reaction with $P_4S_{10}\cdot 4\,Pyr$. Subsequent alkylation with ethyl ω-bromobutyrate leads to the desired β-thiaimino partial structure **47**. Alkylation of the thiolactam **44** with methyl iodide and addition of γ-aminobutyric acid affords the amidine derivative **48**. The lactim ether **46** is easily accessible by alkylating the lactam **43** with ethyl ω-bromobutyrate in the presence of silver oxide. Coumpound **47** proved to have both a platelet aggregation-inhibiting effect and vasodilating activity[92].

By coupling the synthesis of the heterocyclic ring with Corey's $PGF_{2\alpha}$ and prostacyclin syntheses it was possible to prepare β-heteroiminoprostacyclins **19a**—**19c**[63] from **49**, after selection of appropriate protecting groups for the individual synthetic steps (Scheme 7).

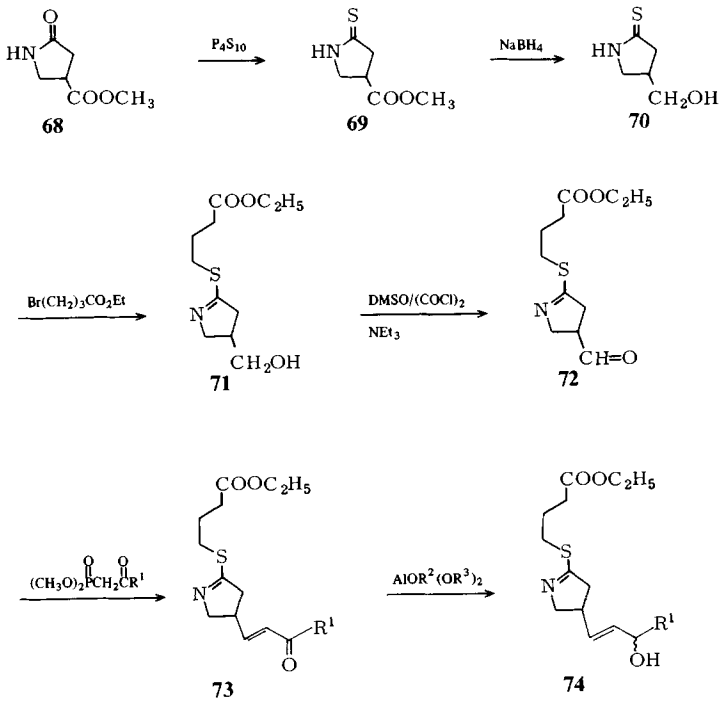


Scheme 7. DMSO = dimethyl sulfoxide; THP = tetrahydropyranyl.

An alternative route to the β-heteroiminoprostaglandins was elaborated, starting from easily accessible bicyclo[3.2.0]hept-2-en-6-one **58** (Scheme 8)[93]. The two key reactions of this synthesis—the nucleophilic attack of lithiodithiane on **59** and the Beckmann rearrangement of **63**—are not totally regioselective; however, the desired products **60** and **64**, respectively, can be easily separated from **61** and **65** by crystallization or column filtration through silica gel.



Scheme 8. NBA = *N*-bromoacetamide, THF = tetrahydrofuran, MST = mesityl.



Scheme 9.

It could also be demonstrated that β-thiaiminoprostacyclins **74** (Scheme 9), having a markedly simplified molecular structure[94], still possessed biological activity. In the synthesis both isomers are formed in the ratio 1 : 1. The Δ^1-pyrrolines obtained induced a decrease in blood pressure, depending on the ω-side chain, following intravenous administration to anesthetized rats ($ED_{25} = 30-100$ μg/kg). There was also an effect on platelet aggregation induced by arachidonic acid, but it was markedly weaker than in the case of PGI_2 (IC_{50}[*] $= 10^{-5}-10^{-6}$ mol/L).

4. Structure-Activity Relationships

Apart from the prostacyclin analogues in which the enol ether group is stabilized or simulated by chemical variations, numerous modifications of the natural prostacyclin and its analogues were prepared in which the ω-side chain is changed[95-97]. Examples of prostacyclins with modified ω-side chain that have an influence on plasma-renin activity, vasodilatation and inhibition of platelet aggregation have been described by *Schölkens et al.*[98,99]. Among such prostacyclin analogues the 10,10-difluoro-13,14-dehydro derivative deserves special mention, because of its increased chemical stability[100]. 12-Fluoro-analogues also exhibit good blood pressure-lowering and platelet aggregation-inhibiting properties[101].

In the series of β-thiaiminoprostacyclins, the following structure-activity relationships were established[102]:

1. An esterification of the carboxyl group in the α-chain generally does not affect the activity, at least *in vitro*.
2. A lengthening or shortening of the α-chain leads to a marked decrease in activity (intravenous studies in rats), which corroborates with the structure-activity relationships found with prostaglandins[2].
3. The ω-side chain can be subjected to various changes. Figure 1 shows that a number of derivatives maintain the blood pressure-decreasing and platelet aggregation-inhibiting effects. Some of the compounds, however, exhibit a greater difference between blood pressure-decreasing activity and platelet aggregation-inhibiting properties than prostacyclin or **19b**, a compound with a biological profile close to that of prostacyclin.

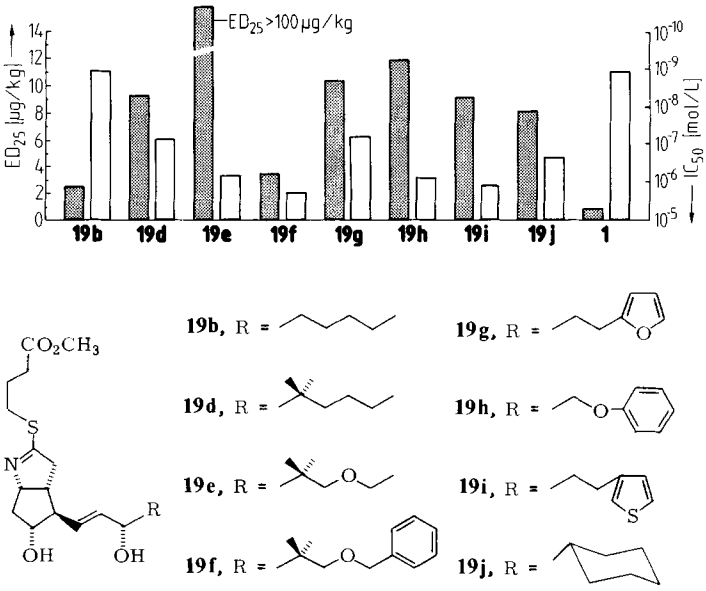


Fig. 1. Decrease in blood-pressure ED_{25} in anesthetized rats (black, left) and inhibition of arachidonic acid-induced platelet aggregation IC_{50} (white, right) by prostacyclin 1 and some β-thiaiminoprostacyclin analogues.

4. As observed with prostacyclin[97], 16,16-dimethyl analogues are usually less active than the basic molecule, in contrast to the corresponding 16,16-dimethyl prostaglandins.

5. Simulation of the Biological Activity of Prostacyclin by Other Compounds with Cardiovascular Activity

Numerous publications describe the pharmacological effects of well-known drugs as being attributable to their influence on prostaglandin, thromboxane, and prostacyclin levels. For example the influence of dipyridamol on prostacyclin biosynthesis[103], the action of antihypertensive agents like reserpine, α-methyldopa and propanolol on the biotransformation of the cyclic endoperoxide PGH_2 into prostacyclin[104], the effect of sodium nitroprusside on the formation of prostacyclin in isolated preparations of heart and vessels[105], and the influence of caffeine salicylate on the PGI_2-dependent inhibition of platelet aggregation[106] have been reported. The blood pressure-decreasing effect

[*] ED_{25} is the effective dose required to decrease the blood pressure by 25%; IC_{50} is the concentration at which the arachidonic acid-induced thrombocyte aggregation is reduced to 50%.

of angiotensin-converting enzyme inhibitors of the Captopril type and the cardiovascular activity of furosemide are possibly also connected with the biosynthesis of prostacyclin[107,108]. A recent article reported that pentoxifylline stimulates[109] microcirculation, which plays an important part in geriatric desease possibly by an increased prostacyclin release. Whether it is possible to stimulate prostacyclin release in patients undergoing chronic therapy still remains to be proven. The entire field of prostaglandin research is developing too rapidly to be able to make an exhaustive survey.

This paper has mainly considered the pharmacological properties and the synthesis of prostacyclin and its analogues. The question of the biochemical mechanism of action was consciously excluded because of its complexity. A detailed discussion would require a comprehensive report on thromboxane (TXA_2) (see Scheme 1), the platelet-aggregating, vasoconstrictive, physiological antagonist of prostacyclin (PGI_2). According to *Gorman*[122]:

The mechanisms responsible for the c-AMP regulatory activity of TXA_2 and PGI_2 are not known—and it is too early to establish the relative importance of the TXA_2 and PGI_2 regulatory systems in the general biochemical control of cells. In cells containing the prostacyclin synthetase, stimulation of the cyclooxygenase may result in an increase in the concentration of c-AMP (inhibition of Ca^{2+} mobilization). It is now of importance to characterize cell types on the basis of their ability to synthetize either TXA_2 or PGI_2. This would provide a much clearer understanding of both the role and mechanism of action of the local hormones, the prostaglandins.

However, great difficulties are encountered[123] when trying to classify the cell types as required by *Gormann*[122]; although it is known that prostaglandin synthesis takes place in discrete renal compartments, informational content of these findings is limited owing to the transport and exchange phenomena occurring mainly in the kidney.

6. Outlook and Conclusion

The above-cited attempt to correlate the function of a single organ—the kidney—with the arachidonic acid metabolism in general and the prostaglandins in particular shows how many factors influence the formation of arachidonic acid metabolites. For this reason, disturbances in the arachidonic acid metabolism are unlikely to be counteracted in general by a diet rich in unsaturated fatty acids, or by inhibition of cyclooxygenase or thromboxane isomerase. It remains to be seen whether a substitution therapy with prostacyclin analogues will be widely applicable and whether the hypothesis is confirmed that classic cardiovascular drugs reveal their effect through a prostacyclin release.

In a progress report on gastrointestinal peptides, *Creutzfeld*[124] has recently made the following statement: "Despite the "explosion" in gastrointestinal peptide research in recent years, clinical application has remained minimal. Such disappointments are not unusual but fairly typical of modern research and should therefore not be considered to be discouraging". This is also true for prostaglandin research.

The list of outstanding medical problems that may be understood through the study of arachidonic acid metabolism remains large, and so from the research point of view, further studies continue to be justified, especially regarding heart attack, stroke, malignant hypertension, deep-vein thrombosis, transplant preservation, vascular surgery, pregnancy-related hypertension, *etc.*

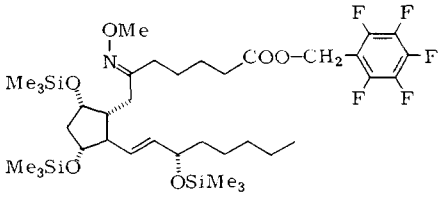
Prostaglandins are the subject of much intensive research work at university and industrial institutions because a knowledge of the metabolism of unsaturated fatty acids is expected to explain at least partially the origin of cardiovascular diseases and arteriosclerosis. A congress entitled "The Second Pharmacological Revolution", dealing, *inter alia*, with prostaglandins has recently come to a close in London. Such a title may sound somewhat euphoric to the prosaic chemist, but admittedly, the discovery of the fatty acid series in general and of prostaglandins in particular—with special consideration of the work on prostacyclin—has brought new developments in the fields of biochemistry and pharmacology. These studies seek a causal therapy of cardiovascular diseases.

7. Addendum

After this manuscript had been completed, the Fifth International Prostaglandin Congress in Florence provided an opportunity to verify the completeness of this review. The more than 800 individual contributions presented at the congress contained a profusion of chemical, biochemical, pharmacological and clinical data which, however, did not reveal any surprising new developments.

The most important results from the Florence meeting together with new publications which appeared whilst the manuscript was in preparation are summarized below under the appropriate headings.

Analytical Procedures: Most recent studies[110] have shown that the methods used up to now for determining PGI_2 in plasma are not specific enough. *Blair et al.*[111] have now reported a new highly selective method for the determination of 6-oxo-$PGF_{1\alpha}$, the stable metabolite of PGI_2 in plasma; the procedure is based on capillary column chromatography coupled with negative-ion chemical ionization mass spectrometry. The 6-oxo-$PGF_{1\alpha}$ is determined as its tris-trimethylsilyl ether **75**; the carboxy group is esterified with pentafluorobenzyl (PFB), the keto group is protected with *O*-methylhydroxylamine.



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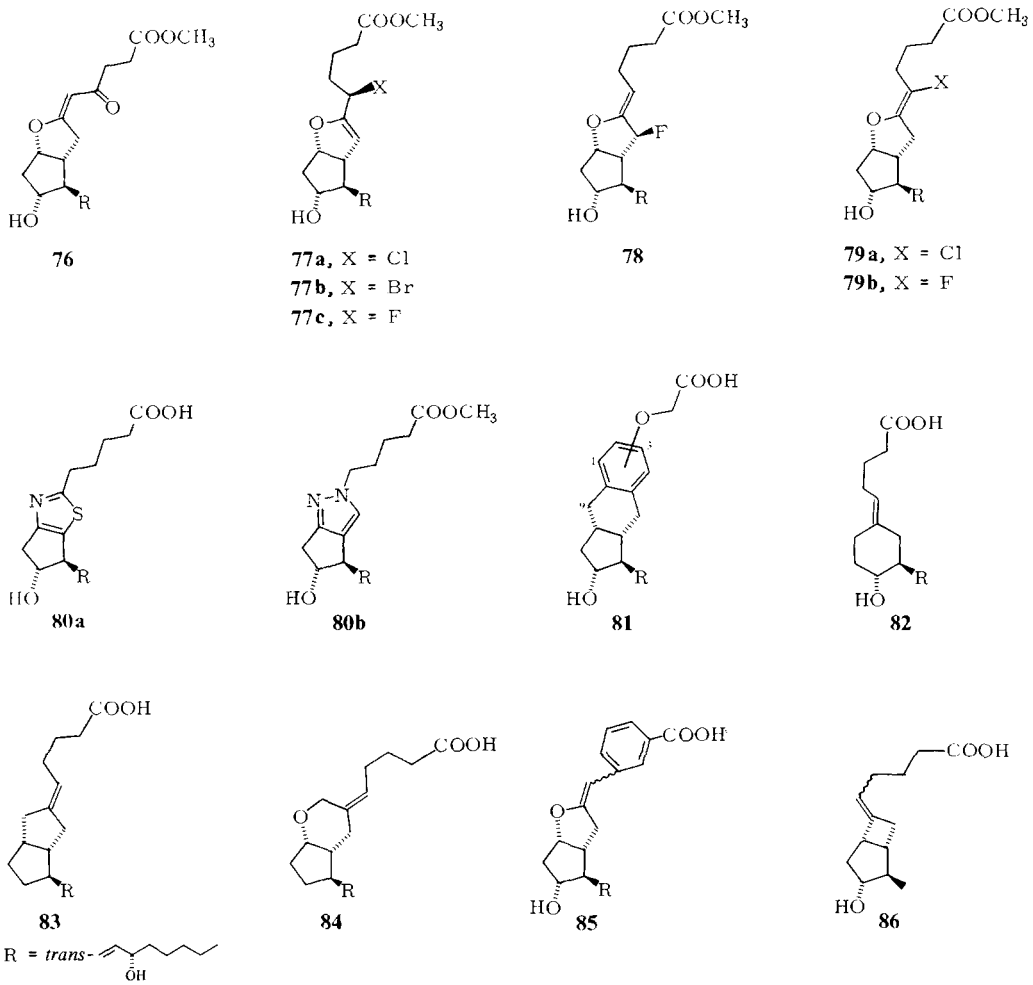
The mass spectrum of this derivative consists of one major ion m/z 614 = [M − PFB] carrying over 50 percent of the total ion current. The sensitivity of this new method is 0.5 pg/mL PGI_2 with 20 mL plasma samples. The assay was employed to determine the plasma level of 6-oxo-$PGF_{1\alpha}$ in



Scheme 10.

20 healthy volunteers. Concentrations in the range 0.5 to 2.49 pg/mL were found. On the basis of these results, *Blair et al.* conclude that PGI_2 does not function as a circulating hormone in man under normal physiological conditions.

Synthetic Prostacyclin Analogues: The following addendum (Scheme 10) gives the state of the art as of June 1982.

In Florence, *Galambos et al.*[112b] presented for the first time the 4-oxo-PGI_2 analogue **76** stabilized by conjugation, as continuation of earlier studies which had resulted in the 7-oxo-PGI_2 analogue **14a**. *Toru et al.*[113] reported the synthesis of stabilized prostacyclin analogues substituted with halogen at position 5 or 7 of the prostacyclin structure (**77a—77c**, **78**, **79a**, and **79b**). *Bradbury*[114] and *Noyori*[115] have meanwhile synthesized two further analogues—**80a** and **80b**—in which the tetrahydrofuran ring of prostacyclin has been replaced by a thiazole or pyrazole ring, respectively. *Aristoff et al.*[116] described the total synthesis of the benzo-annelated derivative **81** which has the side chain in the 1- or 3-position and may have an additional double-bond between positions 8a and 9. *Ceserani et al.*[117] presented a system simplified to the cyclohexane derivative **82**.

Finally, *Gandolfi et al.*[118] reported on a 11-deoxy analogue of carbacyclin **83** and *Dixon et al.*[119] on a further 11-deoxy analogue **84**. Two additional prostacyclin analogues **85** and **86** have been synthesized by *Seipp et al.*[120] and *Newton et al.*[121].

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COMMUNICATIONS

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The Multiple-Path Mechanism for ^{13}C-^{13}C Long-Range Coupling Constants of Bicyclic Hydrocarbons

By *Martin Klessinger** and *Jung-Huyck Cho*

For the interpretation of the ^{13}C-^{13}C long-range coupling constants of cyclic hydrocarbons on the basis of a multiple-path mechanism we have recently assumed an algebraic additivity of the contributions of the various coupling pathways[1]. It should be possible to check this assumption particularly well on bicyclic hydrocarbons in which three coupling pathways are possible for the $J_{1,4}$-coupling between the bridgehead atoms. We have therefore synthesized the unlabeled compounds **1**—**10** and investigated their ^{13}C-NMR spectra. The $J_{1,4}$-coupling constants are collected in Table 1.

The coupling constants of the norbornane and bicyclo[2.2.2]octane series differ by about 5—7 Hz, as is to be expected on replacement of the two-bond coupling pathway *A* by the three-bond pathway *B* on the basis of the increments $^2J_A = -1$ Hz and $^3J_B = 4$ Hz[2]. A comparison of the data for **1**, **2**, and **3**, and for **6**, **7**, and **8**, shows, as expected, that the influence of a methyl group on ^2J_A and ^3J_B can be neglected, while an exocyclic methylene group (pathway C) reduces the coupling by about 2 Hz to $^3J_C = 2$ Hz. The comparison of the coupling constants of **4** and **2** and of **5** and **3**, as well as of **9** and **7** and of **10** and **8** shows that the introduction of a double bond into the norbornane series lowers the coupling by *ca.* 1 Hz, while in the bicyclo[2.2.2]octane series it increases it by *ca.* 1 Hz. This can be explained in terms of the valence angle dependence of the coupling *via* a three-bond pathway.

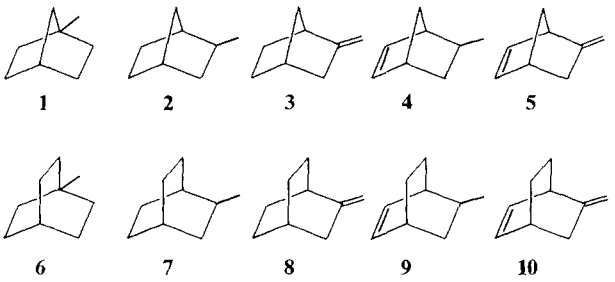

Table 1. Measured and calculated (according to the additivity rule) coupling constants $J_{1,4}$ [Hz] of bicyclic hydrocarbons.

Cpd.	$J_{1,4}$ (exp.) [a]	$J_{1,4}$ (calc.) [b]	Cpd.	$J_{1,4}$ (exp.) [a]	$J_{1,4}$ (calc.) [b]
1	6.8	7	**6**	12.9	12
2	5.9 (*endo*) 6.0 (*exo*)	7	**7**	12.8	12
3	4.4	5	**8**	11.1	10
4	5.5 (*endo*) 5.7 (*exo*)	6	**9**	13.4 (*endo*) 13.3 (*exo*)	13
5	4.0	4	**10**	11.3	11

[a] Measured in C_6D_6 (75%) with a Bruker WM-300 spectrometer at 75.47 MHz in the PFT method. [b] Calculated additively with the increments quoted in the text.

Quantum chemical calculations according to the INDO-SCPT method[4] show that for decreasing CCC valence angles the contribution to the coupling is expected to increase both for the coupling pathway *B* as well as for *D*, the effect in the case of *B* with about 3 Hz for a valence angle change of about 5° being almost twice as large as in the case of *D*[5]. As a result, in the norbornane series the valence angle effect dominates in the case of the saturated system, so that here $^3J_D < {}^3J_B$ and correspondingly a de-

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crease of the coupling $J_{1,4}$ is observed in going from the saturated to the unsaturated system, whereas the opposite behavior is found in the bicyclo[2.2.2]octane series. If, in agreement with these results, one puts $^3J_D = 3$ Hz for the increment of the coupling pathway D for the norbornene derivative and $^3J_D = 5$ Hz for the bicyclo[2.2.2]octene derivative then excellent agreement is found between the measured data and the $J_{1,4}$-coupling constants calculated on the basis of a multiple-path mechanism, also given in Table 1.

Thus, on taking into consideration the ring strain effects an algebraic additivity of the contributions of the various coupling pathways to the coupling constant is strictly fulfilled also in the case of the bicyclic systems. Hence, on using suitable increments the long-range couplings of complicated systems can be estimated, while deviations of the additivity permit conclusions to be drawn regarding ring strain and similar effects.

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[5] M. Klessinger, J.-H. Cho, *Org. Magn. Reson.*, in press; for standard valence angles $^3J_B = 5.46$ Hz and $^3J_D = 4.54$ Hz, whereby according to [2] the calculated value for ^3J_B is to large.

Determination of the Structure of Dimethyldioctadecylammonium Chloride in Solution by Small Angle X-Ray Scattering; Reversible Phase Transition**

By *Hasko H. Paradies**

Phospholipid vesicles are of great importance as models for biological membranes. The use of surfactant vesicles, formed from simple amphiphiles upon sonication, can be anticipated as artificial vesicles mimicking cell membrane functions[1,2]. Dimethyldioctadecylammonium chloride (DODAC, $(CH_3)_2(n\text{-}C_{18}H_{37})_2N^+Cl^-$) and dihexyldecyl phosphate ($(n\text{-}C_{16}H_{33}O)_2P(O)OH$)[4] have been characterized by *Kunitake et al.*[1] and *Fendler*[2]. In spite of their potential for utilization in catalysis, energy conversion, and substrate partitioning no detailed information is available on the size and shape of DODAC surfactant vesicles in solution, nor on the factors which influence them. Unambiguous structural data have been obtained showing the formation of a lamellar bilayer structure as well as the internal structure of DODAC vesicles, including its phase transition behavior under varying pressures and temperatures.

The structural data of DODAC-vesicles (see Table 1) indicate that the amphiphile in aqueous solution is a random distribution of lamellas with a thickness of 4.4 ± 0.2 nm, which is consistent with a hollow vesicular structure with an outer diameter of 35.0 ± 0.1 nm (Fig. 1). The electron density profile perpendicular to the DODAC lamellar plane is shown in figure 1C.

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Table 1. Morphological and hydrodynamic parameters of DODAC vesicles in aqueous solution; pH 7.0; 0.01 mol/L Tris-HCl.

Radius of gyration R_g [nm]	13.8 ± 0.5
Molecular weight $M_r \times 10^5$	33.5 ± 1.5
Thickness of double layer R_t [nm]	4.4 ± 0.05
Degree of hydration [g H_2O/g DODAC]	0.86
Maximum dimension D_{max} [nm]	35.0 ± 0.1
Partial specific volume Φ [mL/g]	0.8561
Diffusion coefficient $D \times 10^{-7}$ [cm^2/s]	1.72 ± 0.05
Mass per unit area [M_r/nm^2]	2510

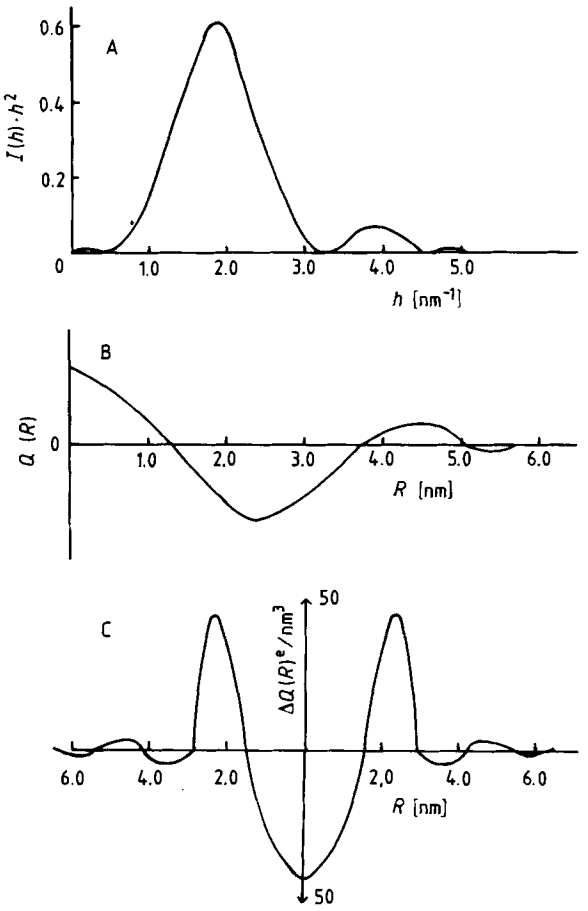

Fig. 1. A) Thickness factor, $I_t(h)h^2$ of DODAC vesicles obtained from the uncorrected data by assuming a one-dimensional cross section distance distribution function: $h = (4\pi/\lambda)\sin\theta$; $\lambda = 1.54$ Å, θ = scattering angle, and $I_t(h)$ = scattering intensity. B) Distance distribution function, $Q(R)$, obtained from the data in Fig. 1A. C) Electron density profile, $\Delta\rho(R)$, across the bilayer thickness obtained from the structure amplitudes.

The results obtained strongly support the view that a certain interdigitation of inner and outer DODAC molecules occurs since the thickness of 4.4 nm is shorter than the length of two octadecyl chains.

DODAC vesicles show a reversible transition at $T_m = 38$ °C at constant pressure and varying temperature, or *vice versa* (Fig. 2). The vesicle sizes changed from $D_{max} = 35$ nm to $D_{max} = 40$ nm, consistent with recent results by *Ceuterick et al.*[4] for dimyristoylphosphatidylcholine[3], but different from those of *Watts et al.*[5].

The changes in the effective hydrodynamic radii R_c ($D_{max}/2$) with pressure and temperature are due to changes in the isopotential partial specific volume from $\Phi = 0.8561 \pm 0.003$ mL/g at 293 K to 0.8361 ± 0.002 mL/g at 303 K. However, DODAC vesicles containing 11%

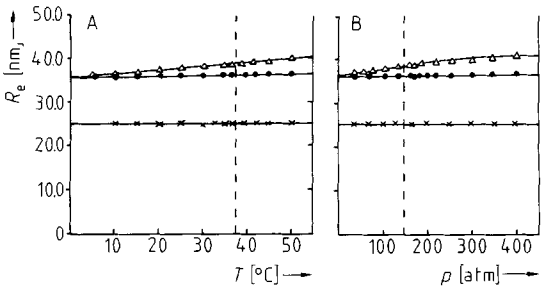

Fig. 2. Effective hydrodynamic radius, R_e, of DODAC-vesicles at 1 atm determined by dynamic light scattering. Temperature-induced phase transition. Broken line: phase transition. •—• DODAC vesicle, ×—× dimyristoylphosphatidylcholine vesicle; △—△ DODAC-vesicle containing 11% (w/w) cholesterol. $R_e = k_B T K^2/(3\pi\eta\Gamma)$; k_B = Boltzmann constant, $\Gamma = (1/\tau_c) = DK^2$ with $K = (4\pi n/\lambda)\sin(\theta/2)$, τ_c = time constant, D = diffusion coefficient: A) temperature-induced phase transition at 1 bar, B) pressure-induced phase transition at 22 °C.

(w/w) cholesterol reveal no changes in the radius of gyration, R_g, sedimentation constant, $S^0_{20,w}$, or diffusion coefficient, D, upon changing temperature or pressure, but in the isopotential partial specific volume from $\Phi = 0.8611$ mL/g to 0.8541 mL/g. Moreover, DODAC vesicles containing 11% (w/w) cholesterol are more stable with respect to pH and passage of ions than those without cholesterol, and they reveal a considerably higher melting temperature ($T_m = 42$ °C). The cholesterol is located close to the quaternary nitrogen.

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CAS Registry numbers:
DODAC, 107-64-2; DMC, 13699-48-4; cholesterol, 57-88-5.

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Photocyclization of 2-Aryl-1,1-difluoroethylenes: Synthesis of Mono- and Difluorinated Polycyclic Arenes

By *René Lapouyade**, *Naïma Hanafi*, and *Jean-Pierre Morand*

Mainly due to their usefulness in biochemistry, the preparation of low-fluorinated compounds remains a problem of current interest[1]. More specifically, fluorinated hydrocarbons have proved to be important tools in defining the metabolic activation pathways responsible for the carcinogenic activity of polycyclic arenes. With the aim of obtaining new conducting radical-ion salts of polycyclic arenes, we were interested in introducing fluorine into these in order to modify their electron-donor properties without seriously affecting their molecular size.

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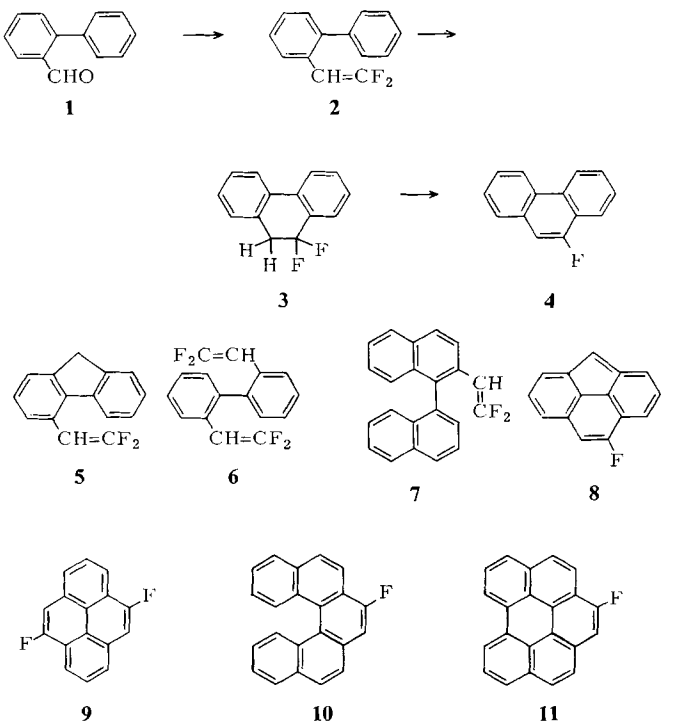
The synthesis of fluorinated polycyclic arenes was based on the first of the following two general methods: synthesis from fluorinated educts or fluorination of arenes. By this means we were able to synthesize arenes **4** and **8**—**10** in good yield and without isomeric impurities. The key step in this sequence is the photocyclization of 2-(2-biphenyl)-1,1-difluoroethylenes, which are accessible by difluoromethylenation of the corresponding aldehydes with the sodium salt of chlorodifluoroacetic acid and triphenylphosphane[2a], or with dibromodifluoromethane, triphenylphosphane and zinc dust[2b]. The final step is a dehydrofluorination carried out by filtration of the irradiated solution on a silica gel column or by reaction with $KOCH_3$ in boiling methanol.

We have now obtained the difluoro compounds **2** and **5**—**7**[3] in 50—80% yield, from which the cyclization products **4** and **8**—**10**[3] (*ca.* 60% yield) were obtained. We have also isolated the intermediate **3** and obtained **11** by oxidative photocyclization of **10**[3]. Since the photocyclization of 2-vinylbiphenyl derivatives is general[4], the reaction described provides a route to a large number of polycyclic arenes fluorinated in a specific position.



1 2 3 4 5 6 7 8 9 10 11

Electrochemical oxidation of **9** gave small black crystals of $\mathbf{9}_2 \cdot PF_6$, **12**[3]; a conductivity of 2 Ω^{-1} cm^{-1} at room temperature was measured along the needle axis using a conventional four probe technique.

Procedure

2: A solution of $ClCF_2CO_2Na$ (1.26 g, 8.3 mmol) in diglyme (6 mL) was added to a stirred hot (160 °C bath temperature) solution of **1** (0.91 g, 5 mmol) and triphenylphosphane (1.57 g, 6 mmol) in 2 mL of diglyme over a period of 35 min. The mixture was heated for 2 h at 160 °C, filtered, and evaporated to dryness and the residue formed was dissolved in CCl_4 and purified by chromatography on silica gel; yield **2** (0.54 g, 53%).

4: A degassed (N_2 stream) solution of **2** (0.092 g) in cyclohexane (85 mL) was irradiated for 24 h ($\lambda = 253$ nm,

Rayonet reactor). After evaporation, the residue was dissolved in 40 mL of a 3×10^{-3} M $KOCH_3/CH_3OH$ solution and refluxed for 1 h. The solution was extracted with ether. After drying, the solvent was removed and the oily residue chromatographed on silica gel with CCl_4. After crystallization from methanol 0.54 g of **4**[5] (60%) was obtained as white needles.

12: A 2×10^{-2} M solution of **9** in CH_2Cl_2, containing nBu$_4$NPF$_6$ (0.15 M) as conducting salt was anodically oxidized under argon at 5 °C with a current of 10 μA. After several hours shiny black crystals of **12** were collected and washed with CH_2Cl_2.

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[3] All the compounds are new and gave satisfactory spectroscopic data and correct elemental analysis or mass spectra.—M.p. and ^{1}H-NMR data (solvent CCl_4, 60 MHz, δ-values, J in Hz). **2**: $\delta = 5.06$ (dd, 1 H, $J_{H^1,H^2\text{-}cis} = 6$, $J_{H^1,H^2\text{-}trans} = 26$), 6.6—7.9 (m, 9 H). **3**: $\delta = 3.63$ (t, 2 H, $J_{HF} = 14$), 6.6—7.93 (m, 8 H). **4**: m.p. = 51 °C; $\delta = 6.99$—7.92 (m, 6 H), 7.92—8.31 (m, 1 H), 8.31–8.87 (m, 2 H). **5**: $\delta = 3.59$ (s, 2 H), 5.57 (dd, 1 H, $J_{H^6,H^7\text{-}cis} = 4$, $J_{H^6,H^7\text{-}trans} = 24$), 6.63—7.32 (m, 6 H), 7.35—7.77 (m, 1 H). **6**: $\delta = 4.76$ (dd, 2 H, $J_{H^1,H^2\text{-}cis} = 5$, $J_{H^1,H^2\text{-}trans} = 25$), 6.53—8.18 (m, 8 H). **7**: $\delta = 4.78$ (dd, 1 H, $J_{H^1,H^2\text{-}cis} = 6$, $J_{H^1,H^2\text{-}trans} = 26$), 6.76—7.98 (m, 13 H). **8**: m.p. = 92 °C; $\delta = 4{,}2$ (s, 2 H); 7—7.9 (m, 7 H). **9**: m.p. = 217 °C; $\delta = 7.42$—9.68 (m, 8 H). **10**: m.p. = 216 °C; $\delta = 6.69$—8.58 (m, 13 H).

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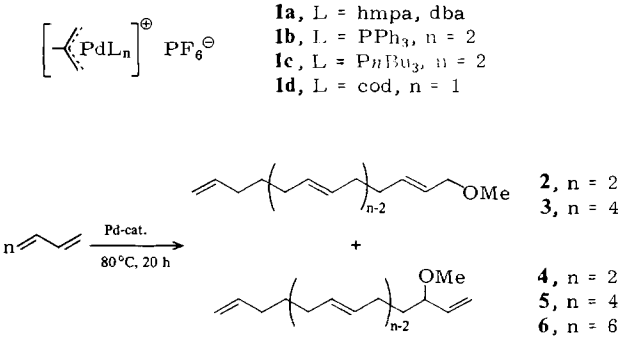
Higher Telomers in the Pd-Catalyzed Reaction of Butadiene with Alcohols**

By *Pierre Grenouillet, Denis Neibecker, Jacques Poirier,* and *Igor Tkatchenko**

Several reports have shown that zero-valent palladium compounds or divalent palladium compounds together with reducing agents are able to catalyze the telomerization of butadiene with a nucleophilic compound ZH (ZH = H_2O, ROH, ArOH, RCOOH, R^1R^2NH, *etc.*) leading to functionalized C_8-products[1]. In very few instances higher telomers containing three or four butadiene units were observed, *e.g.* on using bis[acetato(η^3-allyl)palladium][2a] or mixtures of bis[η^3-allyl(chloro)palladium] and silver salts[2b].



Scheme 1. hmpa = hexamethylphosphoric triamide, dba = dibenzylideneacetone, cod = cyclooctadiene.

We recently reported a method for the synthesis of cationic η^3-allylpalladium complexes which are stabilized by monodentate **1a**—**1c** or bidentate **1d** ligands[3]. On using complex **1a** as catalyst *in situ*, a mixture of $H(C_4H_6)_nOMe$ ethers is formed from butadiene and methanol. Telomers with even numbers n are practically the sole products, the C_{16}-derivative **5** being preferentially formed (Table 1, Scheme 1). Besides **5** and the expected 1- and 3-methoxyoctadienes (**2** and **4**, respectively), compounds **3** and **6** could also be detected. Higher telomers are presumably formed as judged from a preliminary HPLC analysis on μ-Styragel using a 100 Å column.

With the cationic complexes **1b** and **1c** as catalysts—both were isolated in pure form beforehand—mixtures of telomers and oligomers are formed. However, C_8 compounds are now preferred and, furthermore, the higher products do not contain linear oligobutadiene units. Conversely, reactions performed in the presence of complex **1d** give the expected product distribution observed for **1a**. An increase in the molar ratio MeOH : C_4H_6 leads to a greater selectivity for methoxy octadienes. Interestingly, the highest selectivity for C_{16}-derivatives is not observed for the anticipated ratio of 0.25, but for a ratio of *ca.* 0.5. The higher the methanol content the more of **5** is formed.

The temperature and the time of reaction also have a remarkable influence on the product selectivity. With **1a** as catalyst, more than 50% of C_{16}-derivatives is obtained if the reaction is carried out at 60 °C, 6 bar C_4H_6, with a reaction time of 6 h and a MeOH : C_4H_6 ratio of 0.5.

The catalytic reaction observed with methanol proceeds well with other aliphatic alcohols and with phenol; Table 1 shows, however, that the butadiene conversion decreases with increasing steric hindrance of the alkyl group, *i.e.*

Table 1. Telomerization of butadiene in the presence of alcohols ROH or phenol. Reaction conditions: [**1a**] = 0.25 mmol/L; [C_4H_6] = 300 mmol/L; [ROH] = 75 mmol/L; 80 °C 20 h. The upper indices (*e.g.* in C_8^3, C_{16}^5) denote the number of double bonds.

ROH	Butadiene conversion [%]	Product selectivity %							
		C_8^3	C_{16}^5	ROC_8^2	ROC_{12}^3	1-ROC_{16}^4	3-ROC_{16}^4	ROC_{20}^5	ROC_{24}^6
MeOH	94	2	3	20	1	2	32	2	9
EtOH	94	2	3	12	2	2	20	2	9
*i*PrOH	79	3	2	22	—	4	14	—	5
*t*BuOH	38	4	—	17	—	—	—	—	—
C_5H_5OH	45	—	—	10	—	—	—	—	—
PhOH	97	3	—	22	12	3	8	—	—

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Me ≈ Et > *i*-Pr ≫ *t*-Bu[1]. 1-*tert*-Butoxy-2,7-octadiene, which was not obtained with conventional catalysts, is also formed. Higher telomers are formed in all cases except with *t*-BuOH. The presence of large amounts of phenoxy-C_{12}-derivatives may reflect an alteration in the reaction mechanism.

The reaction presumably proceeds *via* condensation of C_8-units, since almost only C_{8n}-products are formed. Indeed, 1-methoxy-2,7-octadiene **2** is converted *inter alia* into the ether **5**. The occurrence of two or even three vacant coordination sites may be a prerequisite for the formation of such higher telomers.

Procedure

All reactions are carried out under argon.
Solution of **1a**: A mixture of $Pd_2(dba)_3 \cdot CHCl_3$[4] (130 mg, 0.125 mmol) and $[(CH_2{=}C(CH_3)CH_2O)P(NMe_2)_3]^{\oplus}PF_6^{\ominus}$[5] (95 mg, 0.25 mmol) is placed in a 50 mL Schlenk tube and degassed by three vacuum-argon atmosphere cycles. Toluene (10 mL) is then added and the reaction mixture stirred under argon for 120 min.

Catalytic reaction: The pale yellow solution is filtered through Celite in order to remove traces of metallic palladium and then transferred *via* a syringe into a glass-lined 100 mL stainless steel autoclave. Methanol (3 mL, 75 mmol) and butadiene (16.2 g, 300 mmol) are then added. The autoclave is stirred magnetically and heated to 80 °C for 20 h; it is then cooled down and the excess butadiene is vented through a cold trap. The conversion is 94%. The products are analyzed by GC with dodecane and eicosane as internal standards.

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[1] a) J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer, Berlin 1980; b) J. Tsuji, *Adv. Organomet. Chem. 17* (1979) 151.
[2] a) D. Medema, R. van Helden, *Recl. Trav. Chim. Pays-Bas 90* (1971) 324; b) Fr. Pat. 2079319 (1971), Mitsubishi Chemical Industries, Ltd.
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[5] D. Neibecker, B. Castro, *J. Organomet. Chem. 134* (1977) 105.

Addition of Alkyl Radicals to Alkynes: Distinction between Radical and Ionic Nucleophiles**

By *Bernd Giese** and *Stephen Lachhein*

In radicals at least one orbital is singly occupied by an electron. This electron hole is filled in radical additions to alkenes by formation of a σ-bond; nevertheless, alkyl radicals are nucleophilic. The apparent contradiction is accounted for by Frontier Orbital theory, according to which the interaction between the highest, singly occupied orbital (SOMO) of the radical and the lowest, unoccupied orbital (LUMO) of the alkene is decisive for the reaction rate[1]. In consequence, the electron density is shifted from the radical to the alkene on the path leading to the transition state. The electron hole on the C-atom of the attacking radical is filled only when the transition state has been crossed. In contrast, with nucleophiles with lone pairs of electrons the negative charge is shifted both in the transition state and in the product to the alkene. This difference is discernible in the gradation in reactivity of alkenes and alkynes in radical and ionic[2] nucleophilic additions. Whereas nucleophiles having lone pairs of electrons attack alkynes markedly faster than alkenes[3], the alkynes in Table 1 react 3.0—5.2 times slower with the nucleophilic alkyl radicals than the corresponding substituted alkenes[4]. The values were obtained by the "mercury method", previously developed by us[1b].

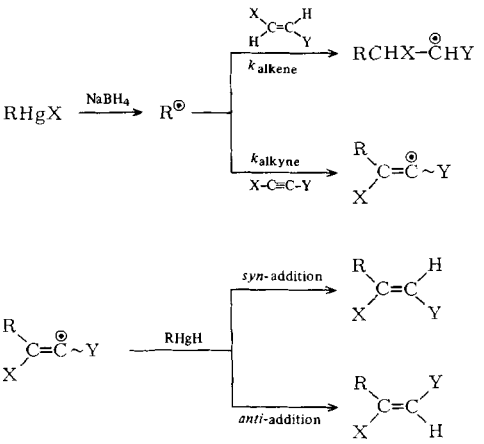

Table 1. Substrate selectivity ($k_{alkene}:k_{alkyne}$) and stereoselectivity (*syn* : *anti*-addition) of alkyl radicals $R^{\odot}$ at 293 K, as well as the overall yields of the addition reactions.

R	X	Y	$k_{alkene}:k_{alkyne}$	*syn* : *anti*	Yield [%]
c-C_6H_{11}	H	C_6H_5	3.5	30 : 70	8
t-C_4H_9	H	C_6H_5	—	7 : 93	10
n-C_6H_{13}	H	CO_2CH_3	—	69 : 31	10
c-C_6H_{11}	H	CO_2CH_3	3.0	56 : 44	35
t-C_4H_9	H	CO_2CH_3	—	28 : 72	41
c-C_6H_{11}	CO_2CH_3	CO_2CH_3	—	64 : 36	21
t-C_4H_9	CO_2CH_3	CO_2CH_3	5.2	42 : 58	54

The lower rate of addition of alkyl radicals to alkynes can be accounted for by the fact that the LUMO of an alkyne is energetically higher than the LUMO of an alkene[5a]. Application of Frontier Orbital theory indicates early transition states in additions of radical nucleophiles. In complete contrast to this, nonradical nucleophiles react faster with alkynes than with alkenes[3], because late transition states are involved and the rehybridization in reactions of alkynes is more energetically favorable than that of alkenes[5a].

Furthermore, the results indicate that, as in alkenes[5b], the *anti*-addition of radicals only predominates when R is highly bulky. This is consistent with the unsymmetrical shielding of the vinyl radical. The *syn*-approach of the H-donor is increasingly hindered as the size of the R group increases.

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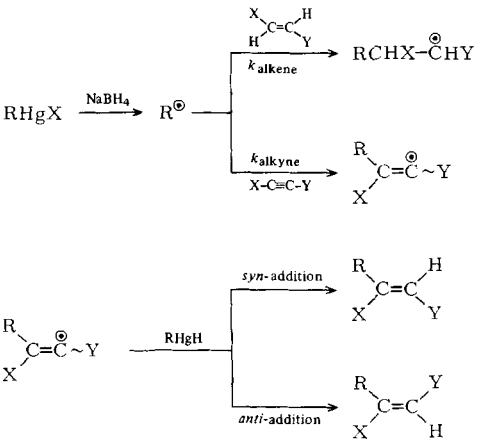

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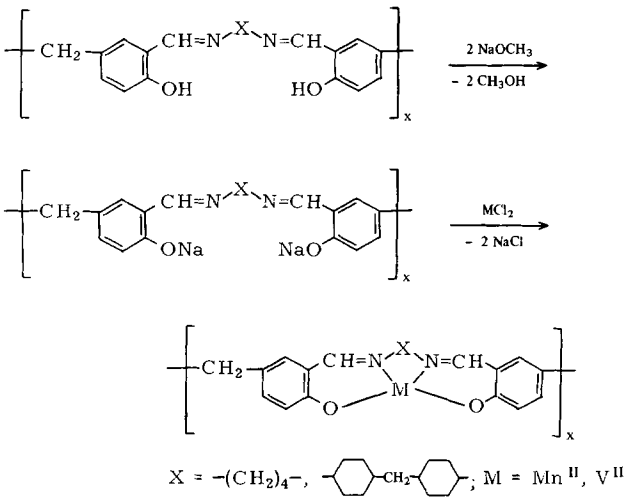
Reversible O_2-Addition to Polymeric Schiff-Base Complexes of V^{II} and Mn^{II} and Their Use as Oxidation Catalysts

By *Wolfgang Sawodny**, *Reinhard Grünes*, and *Helmut Reitzle*

In connection with our investigations on polymeric Schiff-base complexes[1-3] we have now also been able to synthesize such compounds with V^{II} and Mn^{II} as central ion. The complexation reaction proceeds more smoothly and productively *via* a novel route involving the Na-salt as intermediate (Scheme 1).



Scheme 1.

The V^{II}- and Mn^{II}-complexes synthesized according to Scheme 1 take up 0.4—0.5 mol O_2 per mol of complex (determined gravimetrically) at room temperature. The formerly high magnetic moments (*ca.* 5.5 μ_B in the case of the Mn^{II}-complex and 4.5 μ_B in the case of the V^{II}-complex) are reduced by the O_2-uptake. Accordingly, the O_2 is presumably incorporated as a peroxo-bridge between two metal ions. This assumption is supported by the observation that the same oxidized complexes are also formed by direct reaction of the M^{II}-complexes with H_2O_2.

O_2 is taken up reversibly. This is astonishing, especially in the case of the V^{II}-complexes. Thus, not only can the original M^{II}-complexes be recovered by reduction with $N_2H_4 \cdot H_2O$ in CH_3OH, but the O_2 is also liberated in a vacuum at temperatures above 200 °C. This would suggest that these complexes might be good catalysts for oxidation reactions. Preliminary investigations on unsaturated hydrocarbons have shown that the polymeric V^{II}- and Mn^{II}-Schiff-base complexes are as good as, if not even better than, the best previously known metal complex oxidation catalysts (Co^{II}-salene, Fe^{II}-porphyrin complexes)[7].

Table 3. Oxidation of cumene with Mn^{II}-complex (X = —$(CH_2)_4$—) as catalyst; concentration 10^{-3} mol/mol cumene. Reaction time: 15 h (at 30 °C: 65 h). The difference making up 100% consists of small amounts of methylstyrene (< 1%) together with unidentified products.

T [°C]	Cumene I [%]	2-Phenyl-2-propanol II [%]	Acetophenone III [%]	III : II
30	61.9	30.4	2.9	0.09
70	64.1	22.9	7.4	0.32
95	18.2	44	36.7	0.83
105	43.0	27.4	26.7	0.97
120	42.5	24.5	26.6	1.08
150	68.3	7.8	14.3	1.83

In the oxidation of cumene—addition of cumene hydroperoxide as initiator is not necessary here—only traces of the initially formed hydroperoxide[8] are found, evidence that its decomposition is likewise catalyzed by the complex. Generally, the Mn^{II}-complexes are more reactive than the V^{II}-complexes. Oxidation increases with increasing temperature, more and more acetophenone being formed besides 2-phenyl-2-propanol; methylstyrene is also formed in trace amounts. The most favorable temperature is *ca.* 100 °C. At higher temperatures cumene is already oxidized by O_2 without catalysts. Addition of polymeric Schiff-base metal complexes then has an inhibiting effect on the oxidation.

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Electron Density Distribution in the Bonds of the Bridged Bicyclo[1.1.0]butane System 1,5-Dimethyltricyclo[2.1.0.$0^{2,5}$]pentan-3-one

By *Hermann Irgnartinger** and *Annette Goldmann*

The bond between the bridgehead atoms in the bicyclo[1.1.0]butane system is influenced by steric factors and substituent effects[1]. Its properties are considerably different from those of a normal C—C single bond. Using the X—X method[2] we have experimentally determined the electron density distribution in the bonds of the bridged bicyclo[1.1.0]butane system 1,5-dimethyltricyclo[2.1.0.$0^{2,5}$]pentan-3-one **1** from the X-ray data measured at −155 °C. As

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previously found at room temperature[1a], the C3—C3′ bridge bond length (1.417 Å, Fig. 1d) is remarkably short.

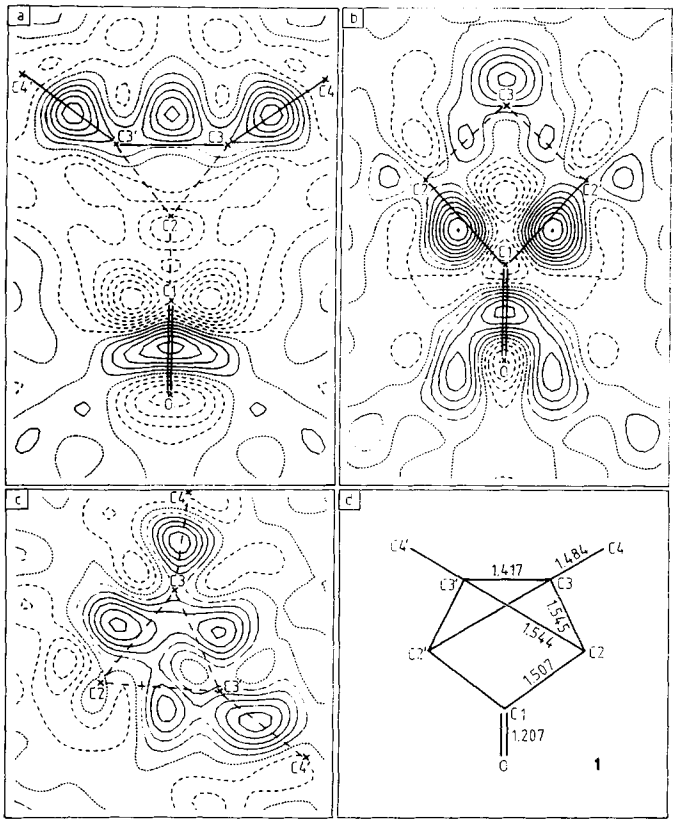

Fig. 1. Electron density distribution in the bonds of **1** and bond lengths [Å] at −155 °C. The contours are drawn at intervals of 0.05 eÅ^{-3} and the standard deviation of the bond lengths is 0.001 Å. The atoms are not numbered in accordance with IUPAC rules. Crystallographic data of **1** (C_7H_8O): for data at room temperature see [1]; at −155 °C: $a = 10.7598(7)$, $b = 6.8256(4)$, $c = 8.396(1)$ Å, $\beta = 110.999(5)°$; $C2/c$; $Z = 4$. Up to $\sin\theta/\lambda = 1.15$ Å^{-1} ($Mo_{K\alpha}$-radiation) 1968 independent, repeatedly measured reflections (248 of which were unobserved, $F_o < 2.5\sigma(F_o)$) were collected; the C and O atoms were refined with 1028 reflections of higher order ($0.70 < \sin\theta/\lambda < 1.15$ Å^{-1}, 27 reflections per variable); $R = 0.036$. The deformation densities are based on 753 ($F_o - F_c$) values taken from the range $\sin\theta/\lambda < 0.7$ Å^{-1}. The carbonyl group in the molecule is located on a crystallographic twofold axis. a) Section through the plane of atoms C1,C3,C3′,C4,C4′,O; b) Section through the plane of the atoms C1,C2,C2′,O; c) Section through the plane of the three density maxima of bonds C2-C3, C2-C3′, and C3-C3′; d) Bond lengths.

All the electron density maxima of the bonds of the tricyclopentane framwork of **1** are clearly displaced outwards from the bond axes, and hence this system consists only of bent bonds. In contrast to a [3.1.1]propellane derivative[3], which also contains the bicyclo[1.1.0]butane moiety —with, however, inverted C-atoms—the electron density in the bridge bond C3—C3′ of **1** clearly stands out, and is displaced by approximately 0.40 Å away from the bond axis (towards the top of Fig. 1a). The electron density exhibits a rotationally symmetric distribution in a section perpendicular to the bond axis (Fig. 1b); below the C3—C3′ bond axis it is equal to zero. Accordingly, no experimental evidence for π character in this bond is found, and it can best be described as a bent σ-bond. All three electron density maxima of the three-membered ring C2, C3, C3′ do *not* lie in the plane of the ring. The C atoms are 0.04 Å (C2) above, and 0.19 (C3) and 0.18 (C3′) Å below the plane through the three electron density maxima (Fig. 1c). The bonds are, therefore, not only bent within the plane of the three-membered ring, but are also twisted out of this plane. The electron densities of the exocyclic bonds, of the C=O bond, of the oxygen atom exhibit no unusual characteristics (Fig. 1).

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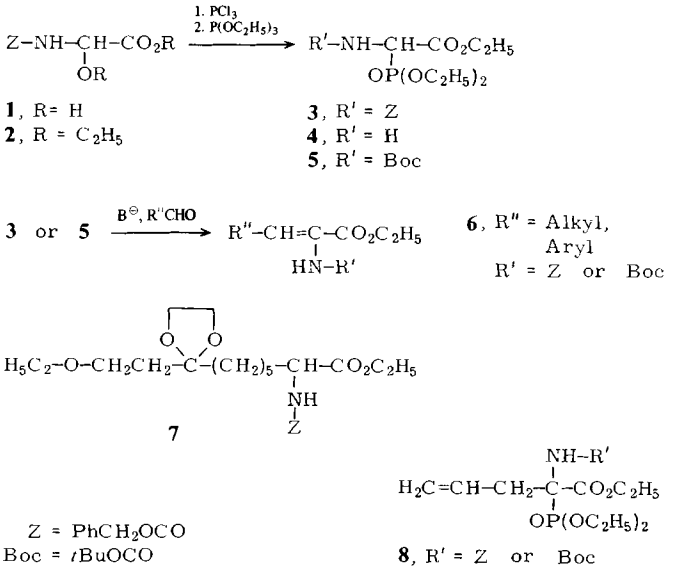
Facile Preparation of *N*-Acyl-2-(diethoxyphosphoryl)glycine Esters and Their Use in the Synthesis of Dehydroamino Acid Esters**

By *Ulrich Schmidt**, *Albrecht Lieberknecht*, *Ute Schanbacher*, *Thomas Beuttler*, and *Jochen Wild*

A phosphorylglycine ester serves as a synthetic building block in the syntheses of cephalosporins[1]. Many methods are known for the preparation of *N*-Acylphosphorylglycine esters; however, none of them are straightforward[1–3]. We describe an effective three-step synthesis of these compounds, which are suitable starting materials for preparation of dehydroamino acids; these in turn can readily be hydrogenated to amino acids with, in many cases, high optical induction. The route shown in Scheme 1 is, therefore, a novel synthesis of amino acids; starting from aldehydes, amino acid esters having two additional carbon atoms or *tert*-butoxycarbonylamino acid esters are formed under mild conditions and, in contrast to almost all other syntheses, an acid hydrolysis step is avoided.



Scheme 1.

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[**] Amino Acids and Peptides, Part 36. Dehydroamino Acids, Part 16.—Part 35: U. Schmidt, M. Dietsche, *Angew. Chem. 94* (1982) 145; *Angew. Chem. Int. Ed. Engl. 21* (1982) 143. This work was supported by the Fonds der Chemischen Industrie and by BASF AG; Part 15: U. Schmidt, E. Öhler, J. Häusler, H. Poisel, *Fortschr. Chem. Org. Naturst. 37* (1979) 251.

Table 1. Synthesis of the dehydroamino acid esters **6**. Method *A*: NaH in THF, room temperature, method *B*: lithium diisopropylamide in THF, −60 °C.

	R″	R′	Method	Yield [%]
6a	C_6H_5	Boc	*A*	73
6b	C_6H_5	Z	*A*	81
6c	2-CH_3O—C_6H_4	Z	*A*	82
6d	2-CH_3O—5-Z-C_6H_3	Z	*A*	85
6e	*n*-C_3H_7	Z	*B*	80
6f	*i*-C_3H_7	Z	*B*	80

The α-hydroxyglycine **1**—readily accessible from glyoxylic acid hydrate and benzyl carbaminate[4]—was converted into the ethyl ether **2**. Successive reaction with PCl_3 and triethyl phosphite led to ethyl 2-benzyloxycarbonylamino-2-diethyloxyphosphorylacetate **3** (yield 80%). *N*-Acyl-2-(diethyloxyphosphoryl)glycine esters having various *N*-protecting groups are accessible by catalytic hydrogenolysis of the protecting group and acylation.

The phosphoryl ester **3** can be metalated by NaH in tetrahydrofuran (THF) and converted in high yields into *N*-benzyloxycarbonyldehydroamino acid esters **6a**–**6d** (Table 1) by condensation with aromatic aldehydes. Steric hindrance of the condensation by *o*-substituents is not observed. For the synthesis of aliphatic dehydroamino acid esters, metalation of **3** with lithium diisopropylamide and condensation with aliphatic aldehydes at −75 °C is the method of choice. By analogy, aromatic and aliphatic *N*-*tert*-butoxycarbonyldehydroamino acid esters are accessible from the phosphoryl ester **5**. The condensation products are formed as *E*/*Z*-mixtures and can be rearranged to afford mainly the (*Z*)-olefins.

The dehydroamino acid esters **6** can be catalytically hydrogenated to the corresponding amino acid esters in quantitative yield. Because of the very mild reaction conditions amino acids with acid-labile functional groups, such as *e.g.* 7 (yield from the corresponding aldehyde: 62%) can be synthesized in this way. The metalated phosphoryl esters **3** and **5** can also be smoothly *C*-alkylated, *e.g.* to **8**.

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[2] J. C. Scopes, A. F. Kluge, J. A. Edwards, *J. Org. Chem. 42* (1977) 376.
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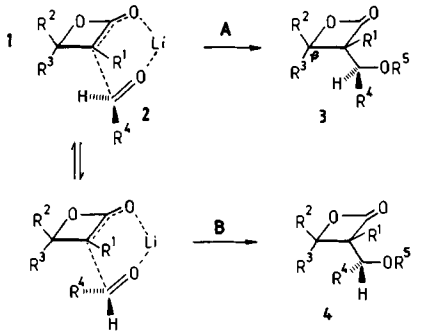
[4] U. Zoller, D. Ben-Ishai, *Tetrahedron 31* (1975) 863.

Three-Center Diastereoselective Aldol Additions of β-Lactone Enolates to Aldehydes**

By *Johann Mulzer** and *Alexander Chucholowski*

We term an aldol addition "three-center diastereoselective" if its course is directed by a chiral center already present in the enolate or carbonyl component. Thereby, the relative configurations of three chiral centers are determined in one addition step. Of the four possible diastereomers, one is formed selectively.

The addition of the β-lactone anions **1** to the aldehydes **2** proceeds with particularly high three-center diastereoselectivity. As a consequence of the rigid, planar ring-structure of **1**, R^2 almost completely shields the *syn*-ring plane against electrophilic attacks[1]. It remains to be clarified whether addition route **A** or **B** is preferred, *i.e.* which of the two possible enantiofacial modes of attacking **2** dominates (Scheme 1).



Scheme 1.

Table 1. Adducts **3** prepared as in Scheme 1. All compounds were characterized by elemental analysis, ^{1}H-NMR, and IR spectra. Yields are between 85 and 95%. R^1 = Ph.

3	R^2	R^3	R^4	R^5	M.p. [°C]	IR (KBr) ν(CO) [cm^{-1}]
a	*t*Bu	H	Ph	$SiMe_3$	174–175	1800
b	*t*Bu	H	Me	H	144–145	1805
c	*t*Bu	H	[a]	$SiMe_3$	204–205	1806
d	*t*Bu	H	[b]	$SiMe_3$	180–185 (decomp.)	1820 1806
e	*t*Bu	H	H	H	145–146 (decomp.)	
f	*i*Pr	H	Ph	$SiMe_3$	159.5–160	1805
g	*i*Pr	H	Me	H	131–132	1810
h	*i*Pr	H	H	H	110–111	1802
i	—$(CH_2)_4$—		Ph	$SiMe_3$	150–153	1792
j	—$(CH_2)_4$—		Me	H	141–145 (decomp.)	1785
k [c]	*t*Bu	H	Ph	$SiMe_3$	107–108	1807

[a] R^4 = [b] R^4 = [c] R^1 = Me

As shown in Table 1, in general up to >95% (^{1}H-NMR analysis of the crude product) of adduct **3** is formed[2]. Only in case **b** is isomer **4** detectable; a product ratio **3b**:**4b** = 85:15 was determined by ^{1}H-NMR spectroscopy. Until an X-ray structural analysis is performed only a tentative configurational assignment for **3b** and **4b** based on IR and ^{1}H-NMR spectroscopic data can be made. The broad OH band in the IR spectrum at 3400 cm^{-1} (CCl_4), which does not dissappear even at high dilution, indicates a hydrogen bonded quasibicyclic chelated structure. This indicates that only in **4b**, but not in **3b**, H^β may be shielded by the side-chain methyl group; this is consistent with the upfield shift of the singlet for H^β in **4b** (δ = 4.45, $CDCl_3$) compared to that in **3b** (δ = 4.71). By analogy, we assume the same configuration as in **3b** is adopted by the remaining adducts of **3**. If this assignment is correct, addition route **A** predominates and the repulsion between R^3 and R^4 outweights that between R^1 and R^4.

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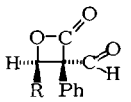
By means of the three-center diastereoselective aldol addition described, the β,β′-dihydroxycarbonyl structural element can be readily prepared in a stereocontrolled manner[3]. It is advantageous for further transformations of **3**



5a, R = *t*Bu
5b, R = *i*Pr

that one of the hydroxy groups is protected in the β-lactone and that the other is free in the side chain; consequently both can be treated differently. For example, we oxidized **3e** and **3h** with chromium trioxide in pyridine to afford the β-lactone aldehydes **5a** and **5b**, novel building blocks with considerable synthetic potential, in quantitative yield.

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[1] J. Mulzer, Th. Kerkmann, *J. Am. Chem. Soc. 102* (1980) 3620, *Angew. Chem. 92* (1980) 470, *Angew. Chem. Int. Ed. Engl. 19* (1980) 466.

[2] The anions **1** were generated as described in [1] from the corresponding β-lactones using lithium diisopropylamide in tetrahydrofuran at −78 °C: 5 min after addition of 2–3 molar equiv. of **2**, the mixture was quenched with 2N H_2SO_4 (R^5 = H) or with chloro(trimethyl)silane (R^5 = $SiMe_3$) and worked-up with water/ether.

[3] Three-center diastereoselective aldol additions to β-lactams: Y. Ueda, A. Martel, J.-P. Daris, B. Belleau, M. Menard, *Can. J. Chem. 60* (1982) 904, and literature cited therein.

7-Azanorbornadiene**

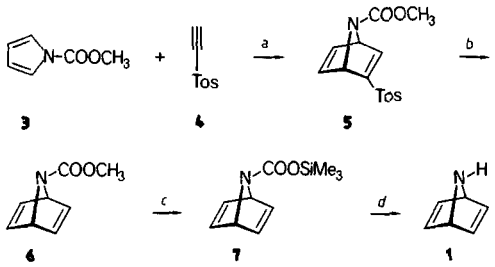
By *Hans-Josef Altenbach, Bernd Blech, Juan Alberto Marco*, and *Emanuel Vogel**

Dedicated to Professor Hermann Stetter on the occasion of his 65th birthday

7-Azanorbornadiene **1**, the parent compound of the multi-substituted 7-azanorbornadienes readily accessible by Diels-Alder reaction of *N*-substituted pyrroles with acetylenedicarboxylic acid esters, is a highly interesting molecule. Its first *C*-unsubstituted derivative, *N*-tosyl-7-azanorbornadiene, was recently synthesized *via* a laborious route by *Prinzbach* and *Babsch*[2]; however, conversion of the tosyl compound into **1** by cleavage of the protecting group proved to be problematic.

Parallels between the structures of **1** and 1,6-imino[10]annulene[3], and their possible chemical consequences stimulated us to synthesize **1**. The synthetic concept which enabled us to prepare **1** rather easily on a preparative scale is shown in Scheme 1.

Adduct **5** (m.p. = 95–96 °C) is formed from ethynyl-*p*-tolylsulfone **4**[4] and *N*-methoxycarbonylpyrrole **3**. Desulfonation of **5** with 6% sodium amalgam[5] affords **6** as a colorless liquid after chromatography on silica gel (ether/pentane) (b.p. = 39 °C/5 × 10^{-5} torr). A moderate yield for **6** (42%) is acceptable, since **5** can easily be prepared in larger amounts. Upon warming with trimethylsilyl iodide, smooth conversion of **6** into the silyl ester **7** occurs[6] (b.p. = 45 °C/5 × 10^{-5} torr) provided that trimethylamine is added to prevent the otherwise rapid acid-catalyzed isomerization of **6** to methoxycarbonylaniline. The silyl ester **7** reacts with methanol *via* the carbamic acid, which can be isolated below −30 °C, to afford the desired **1**, a colorless compound having an amine-like odor and being stable up to *ca.* 80 °C (b.p. = 39 °C/25 torr).



Scheme 1. *a*: 80–85 °C, 24 h; yield 60%. – *b*: 6% Na/Hg, Na_2HPO_4 in THF/CH_3OH (1:1), −78 °C, 3 h; yield 42%. – *c*: $(CH_3)_3SiI$, $(CH_3)_3N$ in $CHCl_3$, 60 °C, 3 h; yield 89%. – *d*: CH_3OH/CH_2Cl_2, reflux, 10 min, yield 80%.

The ^{1}H-NMR spectrum of **1** (90 MHz, $CDCl_3$) exhibits a singlet at $\delta = 2.63$ (N*H*) and two broad singlets at $\delta = 4.73$ (2 tert. H) and 7.06 (4 olef. H), and the ^{13}C-NMR spectrum ($CDCl_3$) signals at $\delta = 66.28$ (C-1,4) and $\delta = 145.57$ (C-2,3,5,6) with $J_{C\text{-}1,H} = 159$ Hz and $J_{C\text{-}2,H} = 180$ Hz. The anticipated fragmentation pattern is observed in the mass spectrum [70 eV: *m/z* 93 (M^+, 8%), 67 ($M^+ - C_2H_2$, 100), 39 ($M^+ - C_3H_4N$, 33)]. The UV spectrum [(CH_3CN), $\lambda = 220$ nm ($\varepsilon = 480$), 252 sh (120)] is very similar to that of 7-oxanorbornadiene.

In contrast to **6**, **1** is not acid sensitive and reacts with hydrogen chloride in ether to give a hydrochloride, which can be recrystallized from acetonitrile [m.p. = 200–201 °C (decomp.)]. **1** is stable to aqueous alkali. Attempts, however, to convert it with butyllithium in tetrahydrofuran (−78 °C) into the lithium salt and to trap this with methyl iodide failed. The expected retro-diene decomposition of **1** into pyrrole and acetylene makes itself noticeable only above 80 °C (half-life determined by NMR spectroscopy in DMSO at 100 °C: 7.5 h). This process is apparently so highly favored that the radical cleavage of one of the C—N-bonds, which would lead *via* benzene imine to 1*H*-azepine or secondary products thereof, has no chance. Conversion of **1** into the *N*-tosylate[2] can be brought about with tosyl chloride (molar ratio 1:1.5) in pyridine (room temperature, 24 h).

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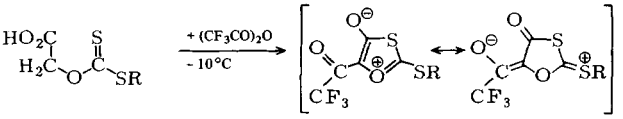
Stable 1,3-Oxathiolylium-4-olates—Synthesis and Cycloadditions of a Novel Class of Mesoionic Heteroarenes**

By *Hans Gotthardt*, Sabine Schoy-Tribbensee,* and *Ulrich Feist*

Mesoionic heteroarenes are valuable synthons for the synthesis of heterocycles[1]. We report here the preparation and cycloadditions of isolable 1,3-oxathiolylium-4-olates of type **2**.

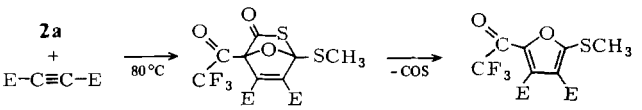
Reaction of methylthio(thiocarbonyloxy)acetic acid **1a** with trifluoroacetic acid anhydride (molar ratio 1:2.17) at −10 °C in ether results in formation of yellow crystals of **2a**[2] in 65% yield after recrystallization from benzene/*n*-hexane (1,3-dithiolylium-4-olate[3a] can be prepared analogously).



1 **2**

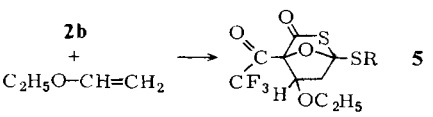
a, R = CH_3; **b**, R = $C(CH_3)_3$

1b reacts analogously to **1a** to afford the mesoionic heteroarene **2b** (37—40%)[2]. The constitutions of **2a** and **2b** are based on their mode of formation, spectroscopic data, and chemical reactions. Until now, mesoionic oxathiolylium derivatives had only been generated *in situ* in [3+2]-cycloadditions[3b].



E = CH_3CO_2 **3** **4**

The novel heteroarenes **2** undergo cycloadditions with activated alkynes and enol ethers. Hence, upon warming to 80 °C in benzene, **2a** reacts with dimethyl acetylenedicarboxylate *via* the non-isolable [3+2] primary adduct **3**, which undergoes elimination of carbon oxysulfide to afford the crystalline 2-trifluoroacetylfuran derivative **4** (68% yield), whose constitution is based on elemental analysis and spectroscopic data[4].



5

The bicyclic primary adduct **5b**[5] from **2b** and ethyl vinyl ether is isolable. Ethyl vinyl ether only forms an oily mixture of isomers with **2a**.

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CAS Registry numbers:
1a, 77274-60-7; **1b**, 82979-46-2; **2a**, 82979-47-3; **2b**, 82979-48-4; **4**, 82979-49-5; **5b**, 82979-50-8; 5-ethoxy-1-(methylthio)-4-(trifluoroacetyl)-7-oxa-2-thiabicyclo[2.2.1]heptan-3-one, 82979-51-9; 6-ethoxy-1-(methylthio)-4-(trifluoroacetyl)-7-oxa-2-thiabicyclo[2.2.1]heptan-3-one, 82979-52-0; trifluoroacetic anhydride, 407-25-0; dimethyl acetylenedicarboxylate, 762-42-5; ethyl vinyl ether, 109-92-2

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[1] Mesoionic arenes: W. Baker, W. D. Ollis, *Q. Rev. Chem. Soc. 11* (1957) 15; M. Ohta, H. Kato in J. P. Snyder: *Nonbenzenoid Aromatics*, Vol. 1, Academic Press, New York 1969, p. 117; W. D. Ollis, C. A. Ramsden, *Adv. Heterocycl. Chem. 19* (1976) 1.

[2] **2a**: M.p. = 103.5—104.5 °C (decomp.); IR ($CHCl_3$): 1740, 1633 cm^{-1} (C=O); UV (cyclohexane): λ_{max} (lgε) = 410 (3.85), 280 nm (4.27); ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): δ = 2.97 (s, SCH_3); ^{19}F-NMR ($CDCl_3$, CCl_3F): δ = −74.8 (s, CF_3). **2b**: M.p. = 56—57 °C (decomp., petroleum ether); IR (CCl_4): 1752, 1640 cm^{-1} (C=O); UV (cyclohexane): λ_{max} (lgε) = 411 (3.60), 284 (sh, 4.02), 266.5 nm (4.28); ^{1}H-NMR (CCl_4): δ = 1.78 (s, $SC(CH_3)_3$); ^{19}F-NMR ($CDCl_3$): δ = −73.2 (s, CF_3).

[3] a) H. Gotthardt, C. M. Weisshuhn, *Chem. Ber. 111* (1978) 2021; b) H. Gotthardt, C. M. Weisshuhn, K. Dörhöfer, *ibid. 111* (1978) 3336.

[4] **4**: M.p. = 112—112.5 °C (cyclohexane); IR (KBr): 1740, 1711, 1702, 1690 cm^{-1} (C=O); ^{1}H-NMR (CCl_4): δ = 2.67 (s, SCH_3), 3.83 (s, OCH_3), 3.91 (s, OCH_3).

[5] **5b**: M.p. = 74—76 °C (petroleum ether); IR (KBr): 1780, 1728 sh, 1709 cm^{-1} (C=O); ^{1}H-NMR (CCl_4): δ = 1.17 (t, J = 7.2 Hz, CH_3), 1.56 (s, $3CH_3$), 2.45, 2.63 (AB of ABX, J_{AB} = 12.8 Hz, CH_2), 3.59, 3.69 (2 q, J = 7.2 Hz, CH_2), 4.33 (X of ABX, J_{AX} = −9.0 Hz, J_{BX} = 3.0 Hz, CH); ^{13}C-NMR ($CDCl_3$): δ = 194.69 (d, J = 5.5 Hz, C=O), 182.81 (dq, J = 38.3 Hz, J = 2.5 Hz, CF_3—C=O), 114.55 (q, J = 292 Hz, CF_3) and additional signals; ^{19}F-NMR ($CDCl_3$): δ = −74.0 (s, CF_3).

Synthesis of Cardiac Glycosides: Evatromonoside and its Anomer**

By *Joachim Thiem** and *Sabine Köpper*

Dedicated to Professor Hans Paulsen on the occasion of his 60th birthday

The cardiac glycosides used in the therapeutic treatment of cardiac insufficiency are still obtained from plant extracts. Due to their structure as oligosaccharides of deoxysugars, particularly of digitoxose, which are linked to a steroid aglycon, such as *e.g.* digitoxigenin, the synthesis of anomerically pure derivatives is more difficult than in the "normal" sugar series[1]. We describe here the glycosidations of novel, reactive derivatives of digitoxose with digitoxigenin.

Glycosidation of D-digitoxal diacetate **1**[2a] with digitoxigenin in acetonitrile using the N-iodosuccinimide (NIS) method[2b] results in exclusive formation of the α-D-glycoside **2**[3a], which can be reductively dehalogenated to afford **3**[3b], and deacetylated to give digitoxigenyl α-D-digitoxoside **4**[3c].

Since, however, the therapeutically more active β-D-anomer is not obtained using this method, we selected another route. Mild acetolysis of methyl α-D-digitoxoside **5** leads to a 1:1 anomeric mixture (72%) of 1,3,4-tri-*O*-acetyl-α- and -β-D-digitoxose, **6**[3d] and **7**[3e], respectively, which can be separated by chromatography. Conversion of this mixture with bromo(trimethyl)silane[4] under extremely mild conditions (R. T., 7 min) leads, for the first time, to the highly reactive 3,4-di-*O*-acetyl-α-D-digitoxosyl bromide **8**[3f] in quantitative yield; at longer reaction times this surprisingly reacts further to afford 4-*O*-acetyl-3-bromo-2,3,6-trideoxy-α-D-arabinohexopyranosyl bromide.

For the glycoside formation, α-acetobromodigitoxose **8** generated *in situ* was allowed to react with digitoxigenin under strict moisture exclusion in the presence of silver carbonate, silver carbonate/silver perchlorate (1:1), or silver silicate[1] in either dichloromethane or in more polar solvent mixtures (nitromethane/toluene/dichloromethane 1:4:2 or 3:7:1) at −40 to 20 °C: the anomeric mixture

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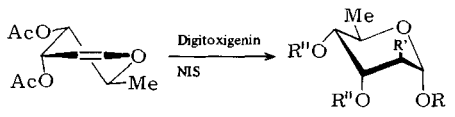
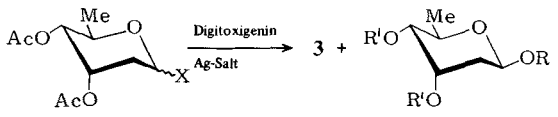
3+**9** (from ^{1}H-NMR *ca.* 1:1.3) was formed in only 10–24% yield after chromatographic purification. The best yields were obtained when the components were treated with silver trifluoromethanesulfonate in nitromethane/toluene/dichloromethane (3:7:1)— the aglycon is just soluble in this mixture—at −78 °C and subsequently warmed to room temperature; in this way **3** and **9** were formed in



1

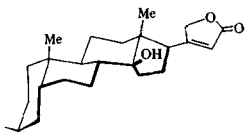
2, R' = I, R'' = Ac
3, R' = H, R'' = Ac
4, R' = R'' = H



5, X = α-OMe
6, X = α-OAc
7, X = β-OAc
8, X = α-Br

9, R' = Ac
10, R' = H

R =



51% yield (ratio 2:3) after chromatography. Simple transesterification finally led to a chromatographically separable mixture of the free glycosides **4** and evatromonoside (digitoxigenyl β-D-digitoxoside) **10**[3g]. Previously, **4** and **10** were each obtained *via* a modified Fischer glycosidation in only 5% yield[5a]. Following the acid-catalyzed transacetalization reaction (cf.[5b]), however, we observed additional elimination of the tertiary 14-hydroxy group in the aglycon leading to formation of the undesired anhydrodigitoxigenin digitoxosides. Thus the procedure presented here provides a more convenient method for the synthesis of complex steroid glycosides of deoxy sugars.

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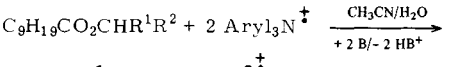
[1] H. Paulsen, *Angew. Chem. 94* (1982) 184; *Angew. Chem. Int. Ed. Engl. 21* (1982) 155.
[2] a) J. Thiem, P. Ossowski, J. Schwentner, *Chem. Ber. 113* (1980) 113; b) J. Thiem, H. Karl, J. Schwentner, *Synthesis 1978*, 696.
[3] a) 86%, m.p. = 79–81 °C, $[\alpha]_D^{20}$ 32.6 ($CHCl_3$): ^{1}H-NMR of the saccharide moiety (C_6D_6): δ = 5.04 (d, 1-H), 4.37 (dd, 2-H), 5.52 (dd, 3-H), 5.39 (dd, 4-H), 4.23 (dq, 5-H), 1.07 (d, CH_3-6); $J_{1,2}$ = 4.5, $J_{2,3}$ = 7.0, $J_{3,4}$ = 3.1, $J_{4,5}$ = 6.2, $J_{5,6}$ = 6.7 Hz; $^4C_1$(D) − : $^1C_4$(D)-conformation ≈ 3:2; b) 61%, syrup, $[\alpha]_D^{20}$ 42.6 ($CHCl_3$); ^{1}H-NMR of the saccharide moiety ($CDCl_3$): δ = 4.85 (dd, 1-H), $J_{1,2a}$ = 3.9, $J_{1,2e}$ = 1.2 Hz); c) 94%, m.p. = 256–258 °C, $[\alpha]_D^{20}$ 85.5 (MeOH, ^{1}H-NMR of the saccharide moiety ($CDCl_3$): δ = 4.99 (dd, 1-H); $J_{1,2a}$ = 3.5, $J_{1,2e}$ = 1.3 Hz); d) syrup, $[\alpha]_D^{20}$ 108.7 ($CHCl_3$); e) m.p. = 90.5 °C, $[\alpha]_D^{20}$ 37.0 ($CHCl_3$); f) ^{1}H-NMR (C_6D_6): δ = 5.96 (dddd ≈ dq, 1-H), 1.70 (mc, 2a-H), 2.19 (ddd, 2e-H), 5.27 (ddd ≈ q, 3-H), 4.60 (dd, 4-H), 4.49 (dq, 5-H), 1.03 (d, CH_3-6), 1.56, 1.61 (s, OAc); $J_{1,2a}$ = 4.9, $J_{1,2e}$ = 0.8, $J_{1,3}$ = 0.7, $J_{1,5}$ = 0.7, $J_{2a,2e}$ = −16.2, $J_{2a,3}$ = 3.0, $J_{2e,3}$ = 2.9, $J_{3,4}$ = 3.0, $J_{4,5}$ = 10.2, $J_{5,6}$ = 6.1 Hz; g) m.p. = 198–200 °C, $[\alpha]_D^{20}$ = −7.0 (MeOH); ^{1}H-NMR of the saccharide moiety ($CDCl_3$): δ = 4.86 (dd, 1-H, $J_{1,2a}$ = 9.5, $J_{1,2e}$ = 2.0 Hz).
[4] J. Thiem, B. Meyer, *Chem. Ber. 113* (1980) 3058, 3975.
[5] a) W. Zorbach, N. Henderson, S. Saeki, *J. Org. Chem. 29* (1964) 2016; b) J. Boivin, C. Monneret, M. Pais, *Tetrahedron Lett. 1978*, 1111.

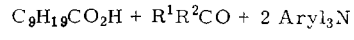
Oxidative Cleavage of Benzyl Esters with Triarylamine Cation Radicals—Selective Deblocking of Protected Carboxy Functions**

By *Steffen Dapperheld* and *Eberhard Steckhan**

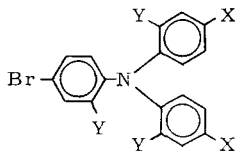
We have been able to considerably extend the possibility of the selective cleavage of benzyl esters—of importance in protective group chemistry—with respect to current procedures[1]. By analog to benzyl ethers[3], benzyl esters are also oxidatively cleaved by stable triarylamine radical cations as electron-transfer agents; these can either be used in stoichiometric amounts as hexachloroantimonates[4] (method *A*) or generated and regenerated anodically in a divided cell from triarylamines (benzyl ester:triarylamine *ca.* 5:1, method *B*, indirect electrolysis). The driving force for the reaction is the deprotonation of the primary-formed ester radical cation.



1 **2**$^+$



3 **4** **2**



2a, X = Br, Y = H
2b, X = Y = Br
2c, X = NO_2, Y = H

4-Methoxybenzyl benzoate reacts with **2b** using method *B* in presence of Na_2CO_3 to afford benzoic acid (94% yield). 2,4-Dimethoxy- and 4-methoxybenzyl esters can readily be cleaved by **2a**$^+$, whereas because of their considerably higher oxidation potential benzhydryl esters are cleaved rapidly only by **2b**$^+$, or **2c**$^+$. Cleavage of unsubstituted benzyl esters is incomplete even by **2b**$^+$ (see also table 2).

The different reactivities of the esters towards **2a**$^+$—**2c**$^+$ can be exploited for the selective deblocking of pro-

Table 2. Oxidative cleavage of substituted benzyl *n*-decanoates **1** by triarylamine radical cations **2**$^+$ (selection).

Educt **1** R^1	R^2	Mediator **2** [a]	Method [b]	Conversion [%]	Yield **3** [%] [c]
2,4-$(MeO)_2C_6H_3$	H	**a**, **b**	*A*	100	83–86 [d]
4-MeO-C_6H_4	H	**a**, **b**	*A*	100	93
4-MeO-C_6H_4	H	**a**	*B*	83	76 (91)
Ph	Ph	**a**	*A*	10	8
Ph	Ph	**b**, **c**	*A* + *B*	100	84–90
Ph	H	**a**	*A* + *B*	0	0
Ph	H	**b**	*B*	82	54 (66)

[a] Standard redox potentials [V] *vs.* standard hyrogen electrode: **2a** + 1.30, **2b** + 1.74, **2c** + 1.63. [b] In moist acetontrile in presence of *ca.* 0.2 g 2,6-dimethylpyridine with 2 mmol **1** for **2a** and *ca.* 1 g $NaHCO_3$ or Na_2CO_3 with 2 mmol **1** for **2b** and **2c**. [c] Isolated yields; values in brackets relative to amount of educt reacted. [d] With 2,4-dimethoxybenzyl esters, method *B* gives more by-products; method *A* is therefore, preferable.

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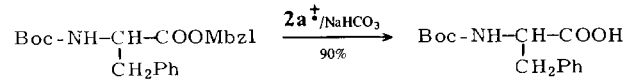
[**] Indirect Electrochemical Processes; Part 12. This work was supported by the Fonds der chemischen Industrie and the Forschungsgemeinschaft.—Part 11: R. Wolf, E. Steckhan, *J. Electroanal. Chem. 130* (1981) 367.

tected carboxy groups. In order to determine the selectivity, competitive experiments on 1:1 mixtures of differently substituted benzyl *n*-decanoates **1** were carried out using method *A*. Thereby it could be shown that not only the substituted benzyl esters (R^1 = 4-MeO—C_6H_4, R^2 = H; R^1 = 2,4-$(MeO)_2C_6H_3$, R^2 = H; $R^1 = R^2$ = Ph) can be deblocked in the presence of unsubstituted benzyl esters (R^1 = Ph, R^2 = H) by **2a**$^+$ or **2b**$^+$ with total selectivity, but that in contrast to previously known methods the acid labile 2,4-dimethoxybenzyl ester group can also be cleaved in the presence of the 4-methoxybenzyl and benzhydryl ester functions by **2a**$^+$, which are also acid labile, in high selectivity (>90%). In this way between 84 and 93% yields of carboxylic acids were obtained upon complete reaction of the more readily oxidizable component. In contrast, despite the large difference in oxidation potentials, no selectivity between 4-methoxybenzyl and benzhydryl esters is found.



Mbzl: 4-Methoxybenzyl–

The *tert*-butyl ester group and the *N*-Boc protecting group—both can be cleaved by acids—do not react with **2a**$^+$ and **2b**$^+$, and hence in presence of these protecting groups 4-methoxybenzyl, 2,4-dimethoxybenzyl, and benzhydryl esters can be selectively cleaved. Furthermore, the Z-protecting group is also stable towards **2a**$^+$/$NaHCO_3$, whereas it is slowly attacked by **2b**$^+$[7].

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CAS Registry numbers:
1, (R' = 2,4-(MeD)$_2$Ph, R^2 = H), 83026-07-7; **1**, (R' = 4-(MeD)Ph, R^2 = H), 83026-08-8; **1**, ($R' = R^2$ = Ph), 83026-09-9; **1**, (R' = Ph, R^2 = H), 42175-41-7; **2a**, 4316-58-9; **2b**, 5489-72-5; **2c**, 83026-10-2.

[1] Th. W. Greene, *Protective Groups in Organic Synthesis*, Wiley, New York 1981, p. 171.

[3] W. Schmidt, E. Steckhan, *Angew. Chem. 90* (1978) 717; *Angew. Chem. Int. Ed. Engl. 17* (1978) 673; *91* (1979), 850, 851 and *18* (1979) 801, 802.

[4] W. Schmidt, E. Steckhan, *Chem. Ber. 113* (1980) 577.

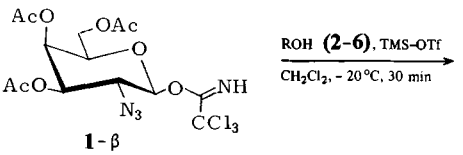
[7] S. Dapperheld, E. Steckhan, unpublished results; experiments to selectively deblock *N*- and *C*-protected amino acids are in progress.

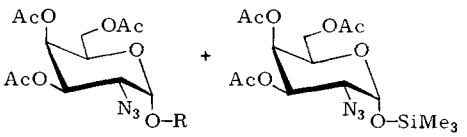
α-Linked Disaccharides from *O*-(β-D-Glycopyranosyl) Trichloroacetimidates using Trimethylsilyl Trifluoromethanesulfonate as Catalyst**

By *Richard R. Schmidt** and *Gerhard Grundler*

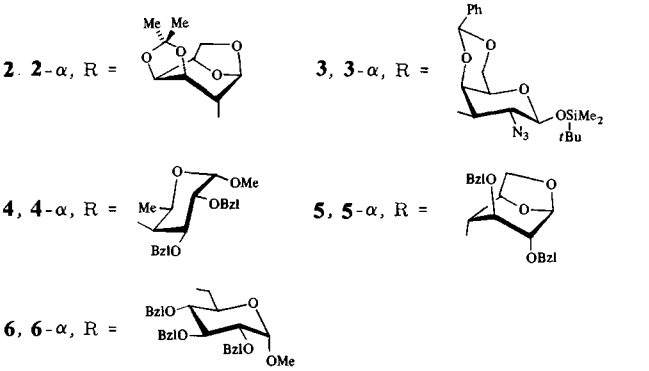
Stereoselective coupling of glycosidic bonds without the use of halogenoses or heavy metal salts as catalysts is of interest for the efficient syntheses of glycosides, and di- and oligosaccharides[1]. The readily accessible *O*-(α-D-glycosyl) trichloroacetimidates of benzyl-protected D-gluco-, D-galacto-, and D-xylopyranoses, as well as D-glucopyranuronic acid ester can be converted under acid-catalyzed conditions, predominantly or exclusively, into β-linked glycosides and β-linked di- and oligosaccharides in good yields[2].

We have now found that *O*-(β-D-glycosyl) trichloroacetimidates react with glycopyranosides containing a free OH group in presence of trimethylsilyl trifluoromethanesulfonate (TMS-OTf) as catalyst[3], to give α-linked disaccharides in good yields. The β-trichloroacetimidate **1**-β, directly accessible from 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactose[5] and trichloroacetonitrile (CH_2Cl_2, K_2CO_3, room temperature, 1.5 h; yield: 55%); $[\alpha]_{578}^{22}$ −4.8, c = 1, $CHCl_3$), reacts with the 2-, 3-, and 4-unprotected glycopyranosides **2**—**5** and TMS-OTf (imidate: alcohol: TMS-OTf = 1.1:1.0:0.04) to give exclusively the biologically important α-linked disaccharides **2**-α-**5**-α[6] (yield, $[\alpha]_{578}^{22}$; **2**-α: 53%, +95.2; **3**-α: 70%, +102.2; **4**-α: 56%, +151.6; **5**-α: 40%, +23.6). As expected, under the same conditions, the D-gluocopyranoside **6**, which contains one primary OH group, reacted to give a higher product yield but lower α-selectivity (yield: 80%; **6**-α:**6**-β = 4:1; **6**α: $[\alpha]_{578}^{22}$ + 112.2, c = 1, $CHCl_3$)[6]. Among others, the trimethylsilyl-α-D-galactopyranoside **7** occurs as a byproduct from which, however, 1-β can be re-isolated.





2-α - **6**-α **7**-α



It is of interest for the mechanism that TMS-OTf also catalyzes the reaction of α-trichlororacetimidate **1**-α (CH_2Cl_2, NaH, room temperature, 1 h; yield 80%, $[\alpha]_{577}^{22}$ + 103.6, c = 1, $CHCl_3$), obtained from 1-**β** by base catalysis, with **2** to afford exclusively the α-linked disaccharide **2**-α (yield: 50%).

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[**] Glycosylimidates, Part 6. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. *G. G.* thanks the Fonds der Chemischen Industrie for financial support.—Part 5: R. R. Schmidt, M. Hoffmann, *Tetrahedron Lett. 23* (1982) 409.

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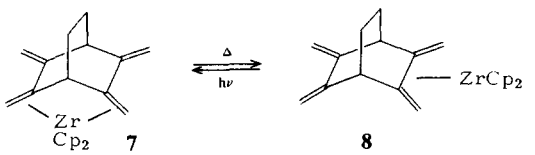
(2,9 : 6,12-η-2,3,5,6-Tetrakis(methylene)-bicyclo[2.2.2]octane)zirconocene, an Isolable Bis(olefin)zirconium(II) Compound**

By *Gerhard Erker**, *Klaus Engel*, and *Pierre Vogel*

The equilibration between bis(olefin)transition-metal complexes and metallacyclopentanes is of great importance for the development of metal-catalyzed processes for the conversion of olefin substrates[1b]. Due to their rapid rearrangement to the more favorable metallacycles, bis(olefin) complexes of group IV transition metals, in contrast to those of other transition metals, have not been observed so far[3]. By using the olefinic ligand 2,3,5,6-tetrakis(methylene)bicyclo[2.2.2]octane **6**[7a], we have now been able to prepare, to our knowledge the first, bis(olefin)zirconocene complex isolable at room temperature.

Bis(η^5-cyclopentadienyl)zirconium(II), generated *in situ* from diphenylzirconocene by photochemically induced reductive elimination of biphenyl[5], reacts with **6** by coordination of the 1,4-diene unit to give the title compound **7**.

7, which is only moderately soluble in the aromatic solvents used, is very sensitive to air and moisture; like haloalkanes, oxygen also liberates the ligand **6**. Thermolysis of **7** (benzene, 60 °C, $\tau_{1/2} \approx 5$ min) leads to formation of its isomer **8**, in which one of the two conjugated diene-units of **6** is bound to the zirconocene group. The bis(olefin)zirconocene complex **7** can be quantitatively recovered upon irradiation (HPK 125, Pyrex filter) of **8** in benzene solution at room temperature.



7 **8**

Tables 1 and 2 (selection). ^{1}H-[^{13}C-]NMR data of the zirconocene complexes **7** and **8** [a].

	7	**8**
=CH$_2$ (free)	4.46, 4.39 br. s (< 1) [96.2 t (157)]	5.13, 4.60 br. s (< 1) [103 t (158)]
=CH$_2$ (compl.)	2.30, −0.02 d (3.6) [17.8 t (152)]	2.51, 0.14 d (11.0 [45.4 dd (130; 145)]
Cp	5.07, 4.68 [104.0, 104.5]	5.50, 5.30 [104.0, 106.0]

[a] C_6D_6, δ rel. TMS, $^2J_{HH}$ [$^1J_{CH}$] in Hz.

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According to the NMR spectra (Tables 1 and 2) **7** is characterized by a markedly much more pronounced π-complex character than **8**. The similarity of the spectra of **7** and those of the previously known mononuclear (*s-trans*-η^4-diene)zirconocene complexes[6] is remarkable. From the finding that **7** can be readily and reversibly converted into a (η^4-diene)metal complex **8** of "normal" structure and stability it appears promising that the observation of other bis(olefin) complexes of early transition metals equilibrating with the isomeric metallacyclopentanes might also be possible.

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[1] b) A. Stockis, R. Hoffmann, *J. Am. Chem. Soc. 102* (1980) 2952.
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Indirect Electrochemical Regeneration of NADH by a Bipyridinerhodium(I) Complex as Electron-Transfer Agent**

By *Rainer Wienkamp* and *Eberhard Steckhan**

Because of its significance in enzyme-catalyzed syntheses, there is considerable interest in straightforward and effective methods for the regeneration of NADH from NAD$^\oplus$. We report here preliminary results on the indirect electrochemical regeneration of NADH from NAD$^\oplus$.

The direct electrochemical reduction of NAD$^\oplus$ at −1.1 V *vs.* SCE leads essentially to inactive dimers and even at −1.8 V, active NADH is only formed in 50% yield[1].

We have now succeeded in reducing NAD$^\oplus$ to NADH using the electrochemically generated two-electron transfer agent [Rh(bpy)$_2$]$^\ominus$, which is generated cathodically from [Rh(bpy)$_3$]$^{3\oplus}$[5]. In this way an enzyme is not required for the transfer of two electrons[2] to the coenzyme. The regenerated NADH is oxidized by cyclohexanone under catalysis of horse liver alcohol-dehydrogenase (HLAD) [eq. (b)].

We performed the reactions in 40–60 mL tris-HCl buffer (pH 9) in divided cells using a graphite cathode, platinum anode, and a glass frit as diaphram at −850 to −950 mV *vs.* Ag/AgCl in discontinuous or continuous working mode [eq. (b)] (Table 1).

In experiment 3, 1.5×10^{-3} mmol of NAD dimer could be determined[1b] corresponding to 0.9% of NAD$^\oplus$ per cycle. At lower working potentials dimerization can be diminished. Using the discontinuous working mode NADH can be separated chromatographically and determined from its absorbance[1b].

The small number of regenerative cycles does not arise from the instability of the electron transfer agent or from that of the coenzyme or enzyme; it results solely from pas-

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[**] Indirect Electrochemical Processes, Part 13. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 12: S. Dapperheld, E. Steckhan, *Angew. Chem. 94* (1982) 785; *Angew. Chem. Int. Ed. Engl. 21* (1982) 1730; *Angew. Chem. Suppl. 1982*, 780

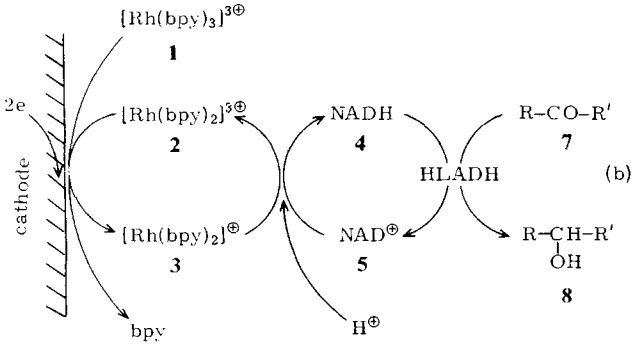

Table 1. Regeneration of NADH from $NAD^{\oplus}$ by electrochemically generated $[Rh(bpy)_2]^{\oplus}$ as electron transfer agent [eq. (b)].

Experiment	Educt [mg] [a] 1	5	7	HLADH [mg]	Product [mg] 8 [b]	Regenerative Cycles $NAD^{\oplus}$/NADH	$Rh^{3\oplus}$/$Rh^{\oplus}$
1 [c]	384 (0.5)	332 (0.5)	59 (0.6)	2.0	25 (0.25)	0.5	0.5
2 [c]	230 (0.3)	398 (0.6)	73.5 (0.75)	2.0	29 (0.29)	0.5	1.0
3 [d]	115 (0.15)	100 (0.15)	96 (0.98)	1.1	33 (0.33)	2.2	2.2
4 [d]	307 (0.4)	133 (0.2)	171 (1.74)	3.9	42 (0.42)	2.1	1.1
5 [d]	192 (0.25)	66.5 (0.1)	110 (1.12)	2.0	29 (0.29)	2.9	1.2

[a] In brackets: mmol. [b] R, R'=—$(CH_2)_5$—; in brackets mmol. [c] Discontinuous process; HLADH and cyclohexanone were added as substrates after electrolysis, cyclohexanol was determined by GC. [d] Continuous process; electrolysis was carried out in presence of cyclohexanone and HLADH.

sivation of the cathode and hence, from the reduction in current which falls off to such a level that the conversion becomes too low. The passivation is caused by formation of a layer which dissolves only slowly in the tris-HCl buffer; elemental analysis of this indicates that $[Rh(bpy)_2(H_2O)_2]Cl$ or $[Rh(bpy)_2(OH)_2]Cl$ is formed. Mechanically cleaning the electrode or using short pulses to positive potentials cause an increase in the current. A Rh^{I}-complex catalyzed hydrogenation of the ketone by cathodically generated hydrogen does not occur—as demontrated by control experiments.

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CAS Registry numbers:
1, 47780-17-6; **2**, 83025-49-4; **3**, 47386-82-3; **4**, 58-68-4; **5**, 53-84-9; cyclohexanone, 108-94-1; cyclohexanol, 108-93-0; alcohol dehydrogenase, 9031-72-5.

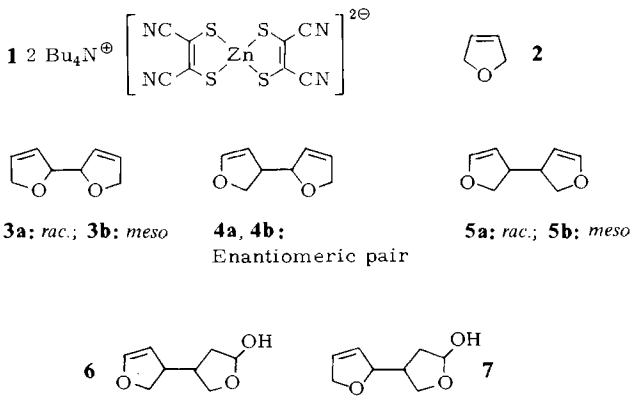
[1] a) C. O. Schmakel, K. S. V. Santhanam, P. J. Elving, *J. Am. Chem. Soc. 97* (1975) 5083; b) H. Jaegfeldt, *Bioelectrochem. Bioenerg. 8* (1981) 355.
[2] H. Simon, H. Günther, J. Bader, W. Tischer, *Angew. Chem. 93* (1981) 897; *Angew. Chem. Int. Ed. Engl. 20* (1981) 861.
[5] M. Kirch, J.-M. Lehn, J.-P. Sauvage, *Helv. Chim. Acta 62* (1979) 1345.

Zinc Sulfide as Catalyst for the Heterogenous Photoreduction of Water

By *Joachim Bücheler, Norbert Zeug,* and *Horst Kisch**

Metal dithiolenes such as **1** in the presence of mild reducing agents enable the hitherto most effective catalytic generation of hydrogen from water with UV light. The actual catalysts are formed in the first reaction step from the complexes. The best system proved to be that of **1** in H_2O/2,5-dihydrofuran **2**[1]. We report here on the mechanism of the reaction and identification of the catalyst as zinc sulfide.

Gas chromatographic analysis of the reaction solution[2] showed that the major products of the oxidation of **2** are **3a, 3b, 4a, b, 5a, 5b**. Their rate of formation correlates with the evolution of H_2 (Fig. 1). Separation of the products was accomplished by preparative GC; the structural assignment is based on GC-MS[3] and 270-MHz ^{1}H-NMR data including extended decoupling experiments. After short irradiation times, only **3a, b** and two new compounds are formed. On the basis of GC-MS and IR data we propose the structures **6** and/or **7** for the new compounds[3].



If the photoreduction is carried out with D_2O[2], pure D_2 is formed initially. However, with increasing conversion HD and H_2 are also formed, while the proportion of D_2 correspondingly decreases: 32% D_2, 50% HD, 18% H_2 after evolution of 2.2 L (0.1 mol) of hydrogen.

These findings point to intermediary OH radicals, which lead to formation of the products **3**—**7**. In the abstraction reaction water is regenerated, leading to formation of HOD and H_2O[4a] if D_2O is used. This explains the change in the isotopic composition of the gas phase. The products **3**—**7** are also obtained by radiolytic generation of OH radicals in H_2O/**2** or by photolysis of H_2O_2 in **2**. In competition experiments with the system **1**/**2**/H_2O/dioxane, the dioxane remains inert, whereas under radiolytic conditions (without **1**) the mixed dehydrodimers are also formed. This confirms the extraordinarily special reactivity of **2** (similarly as for tetrahydrofuran[1]) and indicates that the OH radicals in the catalytic system are not free.

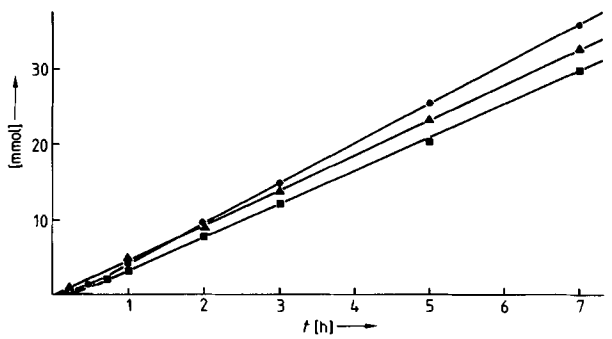


Fig. 1. ●—● hydrogen and ■—■ dehydrodimer formation in the presence of **1**, ▲—▲ hydrogen formation in the presence of 20 mg (0.20 mmol) ZnS [2].

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If the photoreduction is interrupted as soon as **1** is completely decomposed a colorless solid can be isolated by centrifugation. This is found to contain cubic zinc sulfide in a polymer formed from **2**[4b]. Irradiation of a suspension of this solid in $H_2O/2$ leads to the same catalytic photoreduction of water. Zinc sulfide, prepared from zinc sulfate and thiourea, exhibits somewhat the same activity in $H_2O/2$ or H_2O/tetrahydrofuran (Fig. 1). The photocorrosion of zinc sulfide in aqueous systems is apparently hindered by **2** and/or its polymer.

In the system zinc sulfide in $H_2O/2 = 1/14$ (v/v) the quantum yield of the hydrogen formation at 300 nm is 0.1, the reflections of the heterogeneous system not being taken into consideration. A measurable evolution of hydrogen already takes place however at 350 nm, the energy of the band gap (3.54 eV) of cubic zinc sulfide. Colloidal zinc sulfide[5] is much less active.

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1, 18958-61-7; **2**, 1708-29-8; **3a**, 83044-24-0; **3b**, 83044-25-1; **4a**, 83060-37-1; **4b**, 83060-38-2; **5a**, 83044-26-2; **5b**, 83044-27-3; **6**, 83044-28-4; 7, 83044-29-5; $OH^{\bullet}$, 3352-57-6; H_2O, 7732-18-5; ZnS, 1314-98-3

[1] R. Battaglia, R. Henning, H. Kisch, *Z. Naturforsch. B 36* (1981) 396, and references cited therein.

[2] A solution of **1** (50 mg, 0.06 mmol) in $H_2O/2 = 1/14$ (v/v; 120 mL) was irradiated with a Philips HPK 125 W Hg high-pressure lamp ($\lambda \geq 254$ nm) in a quartz immersion lamp apparatus.

[3] Analytical column: CW20M, 70 m, 70—240 °C, 0.9 bar H_2. Identification of **3a** and **3b** and detection of **4a** and **4b** achieved on an optically active column; assignment of **5a**, **5b** so far unsuccessful. Pre-separation into fractions **5a** + **5b** on a Lobar ready-made Si 60 LiChroprep column (40—63 μm), eluent: CH_2Cl_2. Separation of **3a** and **3b** and of **5a** and **5b** by preparative GC: P60/80 mesh, 6 m, 10 mm, 550 mL/min N_2, 100 °C. MS (70 eV, 1 μA, 5 kV, 250 °C) **3**—**7**: base peak $m/z = 69$, MW(CI) **3**—**5**: 138; **6**, **7**: 156. IR (CH_2Cl_2), **6**, **7**: $\nu(OH)_{intramol} = 3390$, $\nu(OH) = 3590$ cm^{-1}.

[4] a) Correspondingly, with large conversions no water consumption was established. b) Follows from analytical and spectroscopic data; we thank Dr. J. Preut, Dortmund, for the Debye-Scherrer photographs.

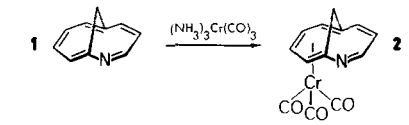
[5] Synthesized according to: Gmelin: *Handbuch der Anorganischen Chemie*, 8th edit., Vol. 32, Verlag Chemie, Leipzig—Berlin 1924, p. 206; A. Henglein et al. also observed only slight activity of colloidal zinc sulfide, private communication 1982; Note added in proof: see also Sh. Yanagida, T. Azuma, H. Sakurai, *Chem. Lett. 1982*, 1069.

Tricarbonyl-2,7-methanoaza[10]annulenechromium(0)

By *Günter Hilken, Tonio Kinkel, Michael Schwamborn, Johann Lex, Hans Schmickler,* and *Emanuel Vogel**

2,7-Methanoaza[10]annulene **1**[1], which has to be considered as an aromatic 10π analogue of pyridine[2], is expected to afford complexes by σ and/or π coordination on reaction with carbonylchromium compounds. Complexation *via* the lone-pair of electrons of the nitrogen atom would correspond to the behavior of pyridine and quinoline, and would lead to a complex with σ bonding between chromium and nitrogen[3]. In contrast, if the 10π electron system acts as the donor, a π complex corresponding to the tricarbonyl-1,6-methano[10]annulenechromium(0) **3**[4] should be formed in which the $(CO)_3Cr$ group is highly probably bonded to the heteroatom-free part of the annulene ring as shown in **2**.

The π complex **2** was obtained as deep-red needles from **1** and triamminetricarbonylchromium (molar ratio 1 : 2) in



refluxing hexane (72 h) [after chromatography on alumina and recrystallization from hexane; sinters above 120 °C; yield 20% relative to amount of **1** reacted; IR (*n*-hexane): 1997, 1941, 1905 cm^{-1} (CO)]. To the best of our knowledge **2**, which is stable in air, is the first transition-metal π complex of an aza[4n + 2]annulene with $n > 1$[5].

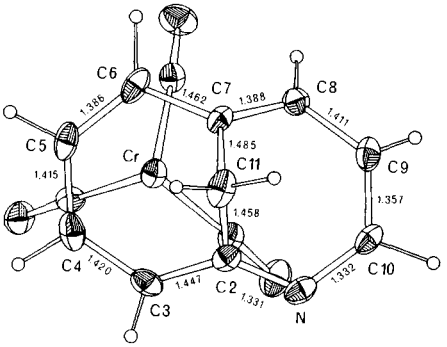


Fig. 2. Molecular structure of **2** in the crystal. Bond lengths in [Å]. C2—C11—C7 94.8 °; C2···C7 2.168 Å.

The unsymmetric bonding of the $(CO)_3Cr$ group to the heteroatom-free part of the annulene ring *anti* to the CH_2 bridge derived from the ^{1}H-NMR parameters of **2**, is corroborated by the X-ray structural analysis (Fig. 2). Whereas in complex **3**[4] the distances of the metal atom to C3, C4, C5, and C6 are almost equal (2.194 to 2.215 Å), in **2** they vary considerably (2.154 to 2.230 Å). The difference in the distances between chromium and C2 and C7 (2.69 and 2.40 Å, respectively) is even more striking. These and other relevant structural data suggest that the previously indicated twisting of the two halves of the annulene ring relative to each other in **1** is increased in the complex. The bond angle of the bridge in **2** (and hence the transannular distance between C2 and C7) is only slightly different from that in **1**, whereas in **3** this angle is markedly smaller than in the free ligand. The delocalization of the 10π electron system in **1** is maintained upon forming the complex, since no alteration of the bond lengths in the aza[10]annulene ring of **2** is observed, despite the fact that the lengths of the C8—C9 and C9—C10 bonds are considerably different. The C—C bond lengths in the complexed part of the ring are in good accord with the corresponding bond lengths in **3**, whereas the N—C bond lengths (as also in derivatives of **1**[2]) are almost identical and are of the pyridine-type. Hence, by analogy to **3**, **2** is characterized as aromatic.

The tendency of **1** to prefer π rather than σ complex formation may be due to the fact that the basicity of **1** is about two pK_a units less than that of pyridine of quinoline.

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CAS Registry number:
2, 82964-01-0

[*] Prof. Dr. E. Vogel, G. Hilken, T. Kinkel, Dr. M. Schwamborn, Dr. J. Lex, Dr. H. Schmickler
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[1] M. Schäfer-Ridder, A. Wagner, M. Schwamborn, H. Schreiner, E. Devrout, E. Vogel, *Angew. Chem. 90* (1978) 894; *Angew. Chem. Int. Ed. Engl. 17* (1978) 853; E. Vogel, *Pure Appl. Chem. 54* (1982) 1015.

[2] For the X-ray structural analysis of 3-bromo-2,7-methanoaza[10]annulene, see R. Destro, M. Simonetta, E. Vogel, *J. Am. Chem. Soc. 103* (1981)

2863; in the meantime structural data are also available for 2,7-methanoaza[10]annulene-3-carboxylic acid and -9-carboxamide (J. Lex, unpublished results).
[3] W. Hieber, F. Mühlbauer, *Z. Anorg. Allg. Chem. 221* (1935) 337; W. Hieber, W. Abeck, H. K. Platzer, *ibid. 280* (1955) 252; W. Strohmeier, G. Matthias, D. von Hobe, *Z. Naturforsch. B 15* (1960) 813.
[4] a) E. O. Fischer, H. Rühle, E. Vogel, W. Grimme, *Angew. Chem. 78* (1966) 548; *Angew. Chem. Int. Ed. Engl. 5* (1966) 518; b) H. Günther, R. Wenzl, W. Grimme, *J. Am. Chem. Soc. 91* (1969) 3808; c) P. E. Baikie, O. S. Mills, *J. Chem. Soc. A 1969*, 328; d) for purposes of comparison the annulene ring atoms in 1,6-methano[10]annulene and in tricarbonyl-1,6-methano[10]annulenechromium(0) **3** are numbered as in **1** and **2**.
[5] For the formation of carbonylchromium π complexes of pyridines, see H.-G. Biedermann, K. Öfele, J. Tajtelbaum, *Z. Naturforsch. B 31* (1976) 321. Dr. K. Öfele is thanked for stimulating discussions.

Synthesis of 2,3,7,8,12,13,17,18-Octamethylporphyrinogen in Almost Quantitative Yield

By *Bernd von Maltzan**

The mode of formation and chemical behavior of the porphyrinogens—including their conformational behavior—are of interest regarding simple syntheses of the porphyrins as well as their biosynthesis[1]. Thus, investigations of the influence of *meso*-substituents on the four strainless conformations of the porphyrinogen ring (Fig. 1)[2a,b] showed that reaction of protons with the four stereoisomers of the *meso*-tetramethyl-*meso*-tetraphenylporphyrinogen formed from acetophenone and pyrrole leads to a stable isomeric equilibrium in which the distribution of isomers is not random but is determined by the influence of the *meso*-substituents on the conformations[2a-c]. Whereas the thermodynamic stability of the uroporphyrinogens I—IV was only indirectly detected *via* the uroporphyrins I—IV[1c], in the reaction of acetophenone with pyrrole the cyclic tetracondensate proves to be the energetically preferred end-product.

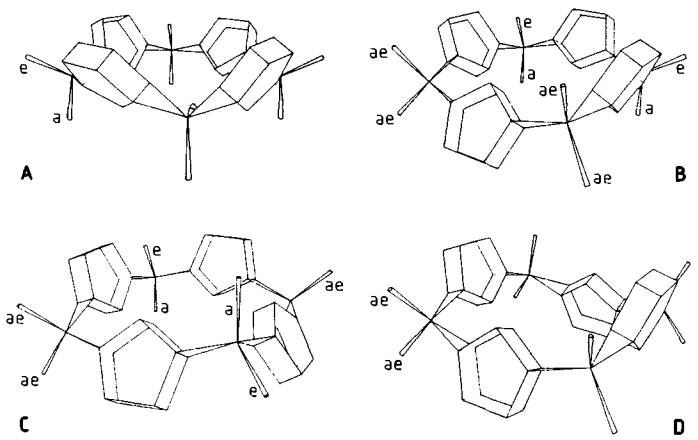
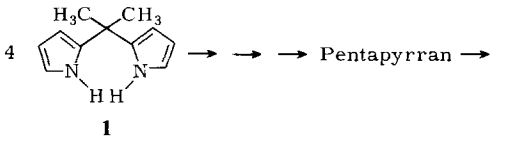
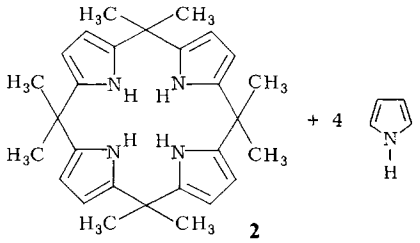


Fig. 1. The four fundamental conformations of the porphyrinogens: "bowl" (**A**), "chair" (**B**), "chaise longe" (**C**), and "saddle" conformation (**D**) (*meso*-substituents: a = axial, e = equatorial or ae = axial-equatorial). The conformations **B**—**D** have been detected X-ray crystallographically [2b].

An additional indication of the preferred formation of porphyrinogens is provided by the ready autocondensation of *meso*-dimethyldipyrrylmethane **1** in boiling ethanol with HCl as catalyst or in CH_2Cl_2/0.1% CF_3COOH to give the known "acetonepyrrole" **2**[1b,c] in 36 and 53% yields, respectively. This must at least proceed *via* open penta- or higher-oligopyrrans, and with cleavage of pyrrole[3a]. Thus, this cyclization is no purely statistically faster[3b] head-to-tail reaction of an open-chain tetrapyrran. Furthermore, the cyclocondensation is also kinetically preferred: If acetone is added according to the dilution principle to pyrrole in boiling methanol with HCl as catalyst, only the porphyrinogen **2** is detectable, even at the beginning of the reaction.

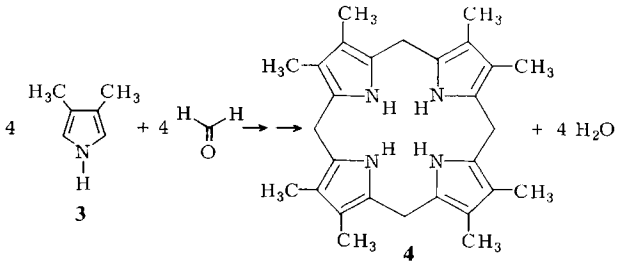


1



2

These findings do not rule out that the corresponding porphyrinogens can also be isolated in the reaction of β-substituted pyrroles with formaldehyde, which furnishes porphyrins in good yield[3c-e]; so far, however, this has been achieved only in the synthesis of the *meso*-tetraphenylporphyrins[3e]. β-Substituted porphyrinogens have had to be synthesized by hydrogenation of the corresponding porphyrins or by acid cyclization of the porphobilinogen-analogous 3,4-dialkyl-2-dimethylaminomethylpyrrole (40–60%)[4a] or of the 3,4-dimethyl-5-hydroxymethyl-2-pyrrolecarboxylic acid (57%)[4b].



3 **4**

Consistent with the strong tendency to undergo cyclization to porphyrinogens, 3,4-dimethylpyrrole **3** reacts with aqueous formaldehyde in methanol at 18 °C with acetic acid as catalyst to give 2,3,7,8,12,13,17,18-octamethylporphyrinogen **4**, which crystallizes chemically pure in practically quantitative (94%) yield (cf. [3c])[5]. **4** is not obtained if the reaction is carried out in boiling solution with conc. HCl or with formaldehyde-diethyl acetal[2d].

The IR spectrum of **4**[5] shows two associated N—H bands besides two "free" ones, even after most intensive drying. Surprisingly, no hydrogen bond forming species such as CH_3OH, H_2O or CH_3COOH were associated, which form strong H bonds above and below the porphyrinogen plane, especially in the "chair" and "chaise longe" forms, but only extremely labile bonds in the "saddle form"[2c]. This points to H-bonds between a pyrrole N—H and a pyrrole unit in a neighboring molecule with modified "chaise longe" or "saddle" form.

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CAS Registry numbers:
3, 822-51-5; **4**, 23016-66-2; formaldehyde, 50-00-0

[1] a) C. Angst, M. Kajiwara, E. Zass, A. Eschenmoser, *Angew. Chem. 92* (1980) 139; *Angew. Chem. Int. Ed. Engl. 19* (1980) 140; b) J. B. Kim, A. D. Adler, F. R. Longo in D. Dolphin: *The Porphyrins, Vol. 1, Part A*, p. 85, Academic Press, New York 1978; c) D. Mauzerall, *ibid.* Vol. 2, p. 91.

[2] a) B. von Maltzan, *Z. Naturforsch.*, in press; b) H. J. Hecht, B. von Maltzan, R. Reinhardt, unpublished; c) B. von Maltzan, *Spectrochim. Acta*, in press; d) *Liebigs Ann. Chem. 1978*, 238.

[3] a) B. Franck, *Angew. Chem. 94* (1982) 327; *Angew. Chem. Int. Ed. Engl. 21* (1982) 343; b) J. H. Fuhrhop, *ibid. 86* (1974) 363 bzw. *13* (1974) 321; c) D. O. Cheng, E. LeGoff, *Tetrahedron Lett. 1977*, 1469; d) A. Treibs, N. Häberle, *Liebigs Ann. Chem. 718* (1968) 183; e) E. Dolphin, *J. Heterocycl. Chem. 7* (1970) 275.

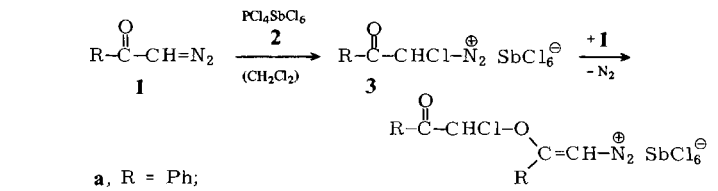
[4] a) H. W. Whitlock, D. H. Buchanan, *Tetrahedron Lett. 1969*, 3711; b) G. V. Ponomarev, R. P. Evstigneeva, N. A. Preobrazhenskii, *J. Org. Chem. USSR 7* (1971) 167.

[5] *Procedure* (all operations carried out under argon): A mixture of 20 mL methanol (p.a.) and 0.5 mL acetic acid (p.a.) was evaporated down to 10 mL and cooled to room temperature, treated with 0.7 mL 35% formaldehyde-H_2O solution and finally 147 mg (1.55 mmol) **3**, and stored in the dark at room temperature. The fine crystals filtered off after 3 h were washed with methanol and dried over P_4O_{10} at 50 °C in a vacuum. Yield 157 mg (94%) **4**, colorless needles, thin-layer chromatographically and ^{1}H-NMR spectroscopically pure (recrystallization from $CHCl_3/CH_3OH$ on exposure to air leads to decomposition); m.p. 234–235 °C (dec.); $R_f = 0.53$ (silica gel-TLC; CH_3Cl/benzene 1:0.5); IR (KBr): 3444.7 (N—H), 3429 (N—H), 3395 (assoc. N—H), 3368 cm^{-1} (assoc. N—H); MS (inlet system temperature *ca.* 140 °C); $m/z = 428$ (M^+; 100%); ^{1}H-NMR ($CDCl_3$): $\delta = 1.95$ (s; 24H), 3.69 (s; 8H), 6.91 (s; 4H).

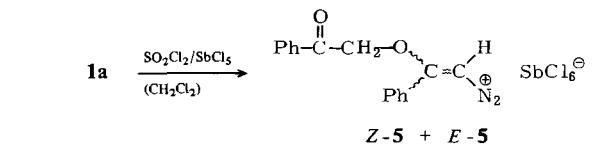
Alkylation of α-Diazoketones with Alkyldiazonium Ions: Facile Synthesis of β-Alkoxyethylenediazonium Salts

By *Kaspar Bott**

β-Alkoxyethylenediazonium salts **4** are readily accessible by allowing tetrachlorophosphonium hexachloroantimonate **2** to react with α-diazoketones **1**. The salts **4** are formed by *O*-alkylation of **1**, whereby the intermediate α-chlorophenacyldiazonium ions **3** resulting from **1** and **2** function as alkylation agents.



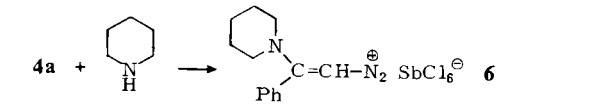
a, R = Ph;
b, R = *p*-$CH_3OC_6H_4$



Z-**5** + *E*-**5**

If instead of **2** a mixture of equimolar amounts of sulfonyl chloride and antimony pentachloride is allowed to react with diazoacetophenone **1a** in dichloromethane, the stereoisomeric olefindiazonium hexachloroantimonates *Z*-**5** and *E*-**5** can be isolated, which in contrast to **4** contain no carbon-bonded chlorine. The phenacyldiazonium ion required for the synthesis of **5** is formed from diazoacetophenone **1a** and hydrogen chloride, although its mode of formation remains to be clarified.

Corresponding to the strongly electrophilic character of olefindiazonium ions[4], **4a** reacts with piperidine, even below 0 °C, exchanging piperidine for the phenacyloxy group to afford the sterically uniform salt **6**. This reaction is associated with a significant shift of the diazo vibrational stretching frequency to longer wavelengths[5].



The preparative importance of the β-alkoxyethylenediazonium salts **4** and **5** lies in their remarkable reactivity, which can be exploited, *e.g.*, to generate unsaturated carbenes[6] or for the low temperature synthesis of triazoles and thiadiazoles[7].

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CAS Registry numbers:
1a, 3282-32-4; **1b**, 6832-17-3; **2**, 18460-56-5; **3a**, 83077-24-1; **3b**, 83077-26-3; **4a**, 83055-28-5; **4b**, 83077-30-9; (*Z*)-**5**, 83077-32-1; (*E*)-**5**, 83077-34-3; **6**, 83077-36-5; $SbCl_5$, 7647-18-9; piperidine, 110-89-4

[4] K. Bott, *Chem. Ber. 108* (1975) 402.

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Photoinitiated Hydrosilations in Presence of Tetrahedral Heterometallic Clusters: Catalysis by Intact Clusters**

By *Charles U. Pittman, Jr.**, *Michael G. Richmond*, *Ma'mun Absi-Halabi*, *Harald Beurich*, *Felix Richter*, and *Heinrich Vahrenkamp**

Many clusters fragment to mononuclear species upon optical irradiation or during thermal catalytic processes. However, there is no definitive evidence demonstrating conclusively that intact clusters serve as active, homogeneous catalysts—although strong evidence does exist in a few cases[1a]. To inhibit cluster fragmentation during catalysis, we advocated the use of transition metal clusters bound by stable, nonfluxional bridging ligands[1].

We have now investigated the photoinitiated hydrosilation of acetophenone with triethylsilane in the presence of the clusters **1**—**7**[2], all of which contain a μ_3-bridging ligand and these clusters have proven to be suitable catalysts for reaction (a) (Table 1).

Both irradiation ($\lambda = 254$ or 355 nm) as well as catalysts are necessary: No reaction occurs in the dark or in the absence of the cluster. Surprisingly, the quantum yields are

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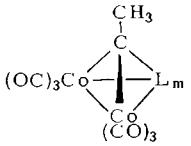
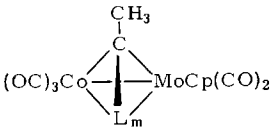
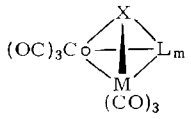
[**] Metal Cluster Catalysis, Part 5. This work was supported by the National Science Foundation (Grant CHE-77-06810).—Part 4: C. U. Pittman, Jr., G. M. Wilemon, W. D. Wilson, R. C. Ryan, *Angew. Chem. 92* (1980) 494; *Angew. Chem. Int. Ed. Engl. 19* (1980) 478.



1, L_m = $MoCp(CO)_2$
2, L_m = NiCp



3, L_m = $Co(CO)_2P(OCH_3)_3$
4, L_m = NiCp

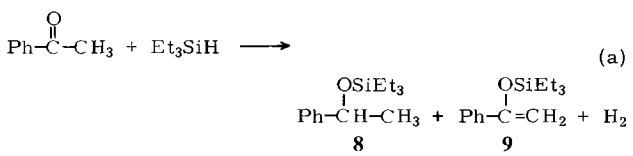


5, X = CH, L_m = $WCp(CO)_2$, M = Co
6, X = S, L_m = $MoCp(CO)_2$, M = Fe
7, X = PPh, L_m = $Fe(CO)_3$, M = Co

Table 1. Photoinitiated hydrosilation [Reaction (a)] with the clusters **1**—**7** as catalysts [a].

Cluster	$\lambda = 254$ nm		$\lambda = 355$ nm	
	Φ [b]	**8**:**9**	Φ [b]	**8**:**9**
1	0.048	[c]	0.016	[c]
2	0.1	[c]	0.01	[c]
3	0.037	[c]	0.014	[c]
4	—	—	0.03	[c]
5	0.028	[c]	0.034	[c]
6	0.45	0.68:1	0.17	0.5:1
7	0.21	[c]	0.03	1.0:1

[a] Reaction after degassing in hermetically sealed Pyrex ampoules ($\lambda = 355$ nm) or in vacuum-tight quartz cells ($\lambda = 254$ nm) at 25 °C. Cluster concentration: 0.01 mol/L; acetophenone: triethylsilane: cluster = 366:366:1. No additional solvent. [b] Φ is the number of moles of product(s) (based on acetophenone consumed) per incident photon. [c] Only **9** was produced.



(a)

greater on using 254-nm radiation than 355-nm radiation. This is to be expected, if the catalytic mechanism requires the loss of carbon monoxide. Lower energy radiation leads to ligand field transitions with occupation of metal-metal σ^* orbitals and, thus, to metal-metal bond cleavage[3]. These bonds readily reform, so that optical absorption rarely leads to productive catalysis. Irradiation with short-wave light effects stronger metal-ligand charge transfer excitation[3], which, in turn, leads to more effective ligand (carbon monoxide) dissociation, and consequently higher catalytic quantum yields.

High performance liquid chromatography (HPLC)[4a] showed that the concentrations of the clusters **1**—**7** do not decrease during the course of the reaction within the limits of detection (*ca.* 0.5%). No other metal-containing complexes could be detected by HPLC or TLC[4b]. Furthermore, after photolysis the clusters **1**—**7** could be recovered in all cases (90—98%) by chromatography on neutral silica gel.

Asymmetric hydrosilation with (+)-**6** would provide irrefutable evidence for the intactness of the chiral FeCoMoS tetrahedron during the reaction. When this reaction was carried out under the conditions given in Table 1 ($\lambda = 355$ nm), after 12 d we were able to isolate a 48% yield of **9**, a 16% yield of racemic **8**, and racemic cluster **6**. We subsequently established that the photoracemization of (+)-**6** at $\lambda = 355$ nm proceeds substantially faster than the hydrosilation reaction.

Even though the asymmetric induction with (+)-**6** failed, the fact that all the clusters were recovered after photolysis strongly suggests that the clusters are indeed the active catalytic species. Moreover, since **1**—**7** all contain stable μ_3-bridging ligands they cannot easily dissociate to mononuclear species[5]. If such fragmentation was to occur, it is difficult to imagine how such fragments could reassemble to regenerate the initial cluster which is isolated at the end of the catalytic reaction.

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[5] Clusters **1**—**7** are stable when irradiated in the presence of H_2 or synthesis gas.

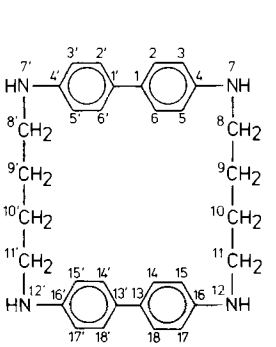
Stetter's Complexes are no Intramolecular Inclusion Compounds

By *Rolf Hilgenfeld* and *Wolfram Saenger**

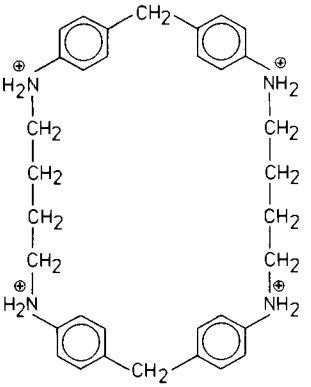
Dedicated to Professor Hermann Stetter on the occasion of his 65th birthday

Host molecules having hydrophobic cavities which can accommodate organic guest species are of interest because of their relevance as enzyme models and their usage for the stabilization and storage of unstable substances. The cyclodextrins, naturally occurring degradation products of starch, have been particularly thoroughly investigated in this field[1].

In recent years, molecules of the phane type have been studied as synthetic models for cyclodextrins[5]. As early as 1955, *Stetter* and *Roos* recognized compounds of this type as potential host molecules[6]. They synthesized bis(*N*,*N*'-tetramethylenebenzidine) **1** and observed that it tenaciously retained benzene or dioxane when crystallized



1



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from these solvents. Based on this and on studies using molecular models, *Stetter* proposed an intramolecular inclusion of benzene (or dioxane) in the cavity of the ligand[6]. Since then, the Stetter complexes have been considered classical examples of intramolecular inclusion compounds[7].

We have now performed an X-ray structure analysis of the benzene complex of **1** and have found that the benzene molecules are *not* accommodated in the central cavities of the ligand molecules but fill interstices between them (Fig. 1). Thus the complex does not represent an intramolecular inclusion compound as hitherto assumed. Moreover, it contains only half a mole of benzene per mol of **1**, since the benzene molecule is localized on a crystallographic center of symmetry.

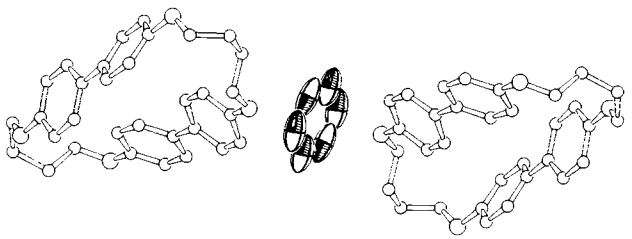

Fig. 1. Structure of the benzene complex of **1** in the crystal. The benzene molecule occupies a center of inversion between two ligand molecules.

The conformation of **1** in the crystal structure precludes intramolecular inclusion of a guest molecule: The benzidine moieties are not parallel but approximately perpendicular to one another and hence cannot function as the walls of an intramolecular cavity. As is usual for benzidines, the phenyl rings in both moieties are twisted about the biphenyl pivot bond by 23.1° and 28.0°, respectively. In contrast, inclusion of benzene in the molecular cavity corresponding to Stetter's model concept[6] would require strictly parallel alignment of the biphenyl skeletons. Moreover, each of the latter would have to adopt a non-twisted, coplanar conformation leading to unfavorable interactions between the *ortho* hydrogen atoms (H2,H2′; H6,H6′) of adjacent phenyl rings.

From these results we conclude that, in contrast to the opinion of *Faust* and *Pallas*[16], the structurally similar ligands employing binaphthyl instead of biphenyl spacers do not form intramolecular inclusion complexes either. However, in case of the related ligand **2**, *intra*molecular inclusion of a guest molecule has been established by X-ray structure analysis[17]. In this complex, a durene molecule is located at the center of the almost rectangular host cavity. This is due to subtle, but important differences in molecular structure: **2** contains diphenylmethane instead of biphenyl moieties. The methylene carbons of the former provide two of the four corners of the rectangular cavity—a configuration which could never be adopted by the biphenyl units of **1**. Moreover, in contrast to **1**, the amino nitrogens of **2** are protonated, rendering **2** not only water soluble but also more flexible than **1**, so that two of the amino groups can form the remaining two corners of the rectangular cavity. The effect of protonation of **1** on its conformational flexibility remains to be determined.

Our results show that subtle changes of molecular structure may result in a completely different inclusion behavior of a potential host molecule. This is due to the complicated interplay of weak intermolecular forces that govern host-guest interactions, which usually cannot be understood by simple studies using space-filling models.

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The complete manuscript of this communication appears in: *Angew. Chem. Suppl. 1982*, 1690-1701

CAS Registry number:
1 · 05 benzene, 83077-42-3

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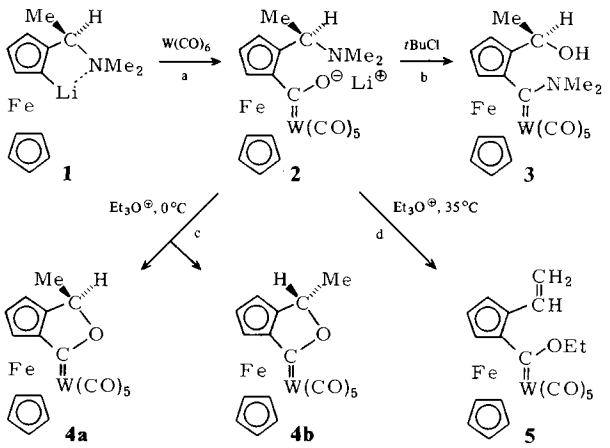
Chiral Binuclear Carbene Complexes from (*R,R*)-1-(1-Dimethylaminoethyl)-2-lithioferrocene and Hexacarbonyltungsten**

By *Rudolf Hermann* and *Ivar Ugi**

Dedicated to Professor Hermann Stetter on the occasion of his 65th birthday

The chiral binuclear carbene complexes **3**, **4a**, **4b** and **5** are obtained by reacting (*R,R*)-1-(1-dimethylaminoethyl)-2-lithioferrocene[6] with hexacarbonyl tungsten. The relative yields of the products depend on the reaction conditions and additives (Scheme 1). It is noteworthy that **1**, the reaction partner of hexacarbonyl tungsten, contains both functionalities which are needed for forming the carbene complex[1].



Scheme 1. a: Et_2O, 0 °C; b: yield *ca.* 25% **3**; c: $Et_3O[BF_4]$ or FSO_2Me, 20 h, yield *ca.* 15% diastereomeric mixture **4a/4b** (81:19); d: analogous to c, but heating under reflux, yield *ca.* 10% **4a/4b** together with 4% **5**.

The intermediate **2** is converted into **3** in the presence of proton donors like *tert*-butyl chloride. For such reactions an unusual mechanism seems to be plausible: the ex-

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change of the hydroxy group and the dimethylamino group is likely to proceed *via* the intermediacy of a carbyne complex. The Me_2N-group, which normally has no nucleofugual properties, serves here as the leaving group of an alkylating system.

The formation of the diastereoisomeric furanoid carbene complexes **4a** and **4b** (81:19, NMR) is favored at 0 °C in the presence of strong alkylating agents such as triethyloxonium tetrafluoroborate, whereas at 35 °C predominantly **5** is produced. The conversion of **2** into **4b** deserves special mention, since, to our knowledge, it is so far the only exception to the customarily retentive course of nucleophilic substitutions in α-ferrocenylalkyl compounds[11].

All the reaction products have been isolated, and have been identified by elemental analysis and spectroscopic data MS, IR NMR). The ^{13}C-NMR chemical shift of the "carbene carbon atom" of **3** has the comparatively low δ value of 213.36. The chemical shift and the coupling constant ($J_{183W\text{-}13C} = 126.4$ Hz) of the carbonyl carbon atoms of **4** and also of the other products are well within a range which is typical for carbene complexes[1].

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The complete manuscript of this communication appears in: *Angew. Chem. Suppl. 1982*, 1630–1642

CAS Registry numbers:
1, 83095-39-0; **2**, 83095-40-3; **3**, 83095-41-4; **4a**, 83095-42-5; **4b**, 83149-19-3; **5**, 83095-43-6

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"γ-$PW_{12}O_{40}^{3-}$", A Heteropolyanion with Clathrate Character

By *Joachim Fuchs**, *Axel Thiele*, and *Rosemarie Palm*

The majority of the numerous heteropolyanions of composition $XM_{12}O_{40}^{z-}$ (M = Mo, W; X = P, Si, B *etc.*), adopt the so-called Keggin structure (α-type)[1]: Four M_3O_{13} groups consisting of MO_6 octahedra tetrahedrally surround the heteroatom X (Fig. 1a). An isomeric β-type is also known in which one of the M_3O_{13} groups is rotated by 60°[2]. We have now discovered, in the course of structural studies on tetraalkylammonium tungstophosphates, a novel anion with centrosymmetric tungsten sites, for which we propose the designation γ-type.

Precipitation of commercial phosphotungstic acid with tetrabutylammonium bromide in aqueous solution results in formation of an α-dodecatungstophosphate, $[N(C_4H_9)_4]_3PW_{12}O_{40}$, which can be recrystallized from acetone: monoclinic, space group $P2_1/c$ with $a = 14.86(1)$, $b = 25.08(1)$, $c = 22.91(1)$ Å, $\beta = 93.37(8)°$, $V = 8526.3$ Å^3, $Z = 4$. The isomeric γ-compound is obtained in a secondary reaction. Acidification of an aqueous solution of Na_2WO_4 and Na_2HPO_4 (molar ratio 3:1) with glacial acetic acid and precipitation with tetrabutylammonium bromide results first in formation of $[N(C_4H_9)_4]_4H_3PW_{11}O_{39}$, which can be recrystallized, undecomposed, from isobutyl methyl ketone. In contrast, the γ-dodecatungstophosphate crystallizes from ethanol-acetone. The triclinic compound, space group $P\bar{1}$, has lattice parameters $a = 15.410(9)$, $b = 19.535(7)$, $c = 13.897(6)$ Å, $\alpha = 87.12(3)$, $\beta = 90.46(4)$, $\gamma = 84.89(4)°$, $V = 4161.3$ Å^3, $Z = 2$. Its anion is built up from WO_5 units (tetragonal pyramids) and consists of a neutral $W_{12}O_{36}$ moiety (Fig. 1b), in the cavity of which a PO_4^{3-} anion is incorporated.

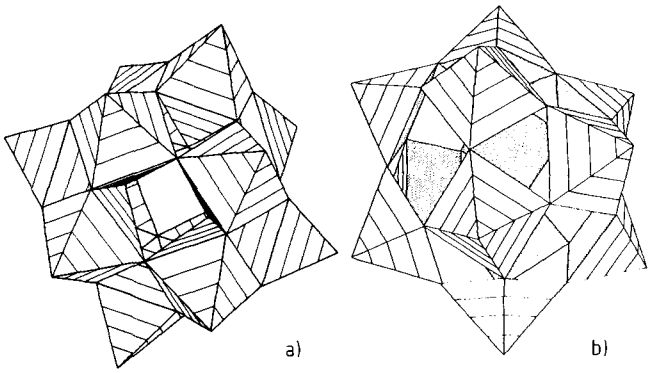

Fig. 1. a) $W_{12}O_{40}$ framework of α-$PW_{12}O_{40}^{3-}$; b) $W_{12}O_{36}$ framework of γ-$PW_{12}O_{40}^{3-}$.

In the unit cell the two anions with phosphorus atoms at 0, 0, 0 and ½, ½, ½ are differently orientated. It differs markedly from the α-type in the positions of the tungsten atoms, each of which occupies the corner of a cuboctahedron, which, however, in the case of the α-type is tetrahedrally distorted (Fig. 2a): the WW distances within the edge-bridged WO_6 octahedron (small dotted triangles) are, on average, 340 pm, within the vertex-linked (large dotted triangles) 369 pm. In contrast, in the γ-type (Fig. 2b) they are all *ca.* 356 pm. Here, the cavity has almost cubic symmetry and, hence, offers two equivalent positions for tetrahedra, which are statistically occupied in the crystal[3].

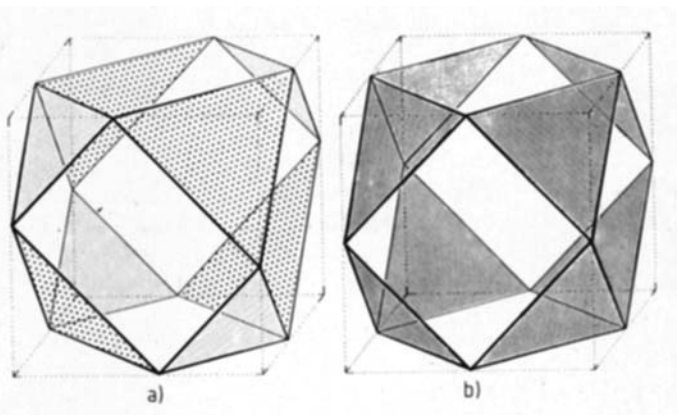

Fig. 2. Positions of the tungsten atoms in α-type (a) and γ-type (b) of $PW_{12}O_{40}^{3-}$.

The novel anion is to be considered as a clathrate; incorporation of the phosphate O atoms in the coordination sphere of the N atoms must lead to removal of the center of symmetry, because then, as in the α-type, vertex- and edge-linked octahedral groups, respectively, would face each other.

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[**] *Note added in proof*: The isotypic γ-tungstoarsenate has also been prepared: H. Neubert, J. Fuchs, unpublished results.

In the γ-type every tungsten atom is bonded to a terminal (O_t) and to four bridging oxygen atoms (O_b). The distances W—O_t = 166 pm and W—O_b = 191 pm do not differ significantly from the analogous distances in the α-type. In contrast, the P—W distance of 355.8 pm is markedly shorter than in the α-form.

The isopolyanion $H_3W_{12}O_{40}^{5-}$[4a] has the α-structure, just as the heteropolyanions $CuW_{12}O_{40}^{7-}$ and $CoW_{12}O_{40}^{5-}$[4b], in which even Cu^+ and Co^{3+}, respectively, are forced to adopt the unusual tetrahedral coordination. The existence of the centrosymmetric γ-type with a heteroatom, which itself strives for tetrahedral cooordination is, therefore, all the more notable[**].

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$[N(C_4H_9)_4]_3PW_{12}O_{40}$, 53749-37-4; $[N(C_4H_9)_4]_4H_3PW_{11}O_{39}$, 68694-94-0; Na_2HPO_4, 7558-79-4; Na_2WO_4, 13472-45-2.

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Novel Synthetic Building Blocks Activated by Ring Strain: General Entry to 2-Chloro-2-cyclopropylidene Acetates**

By *Thomas Liese, Gisela Splettstösser,* and *Armin de Meijere**

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

The cyclopropane ring is finding ever increasing use as functional and/or reactivity-increasing group in the design of organic syntheses[1]. Promisingly versatile are the esters **5**, for which we have now found a convenient and general synthesis.

When heated with potassium hydroxide and methanol, the 1-chloro-1-(trichlorovinyl)cyclopropanes **1**[2,3]—which are readily accessible from olefins and tetrachlorocyclopropene—afford the orthoesters **2** in good yields (see Table 1). On acid-catalyzed hydrolysis, the ortho esters **2** are smoothly and quantitatively converted into the 2-chloro-2-cyclopropylidene acetates **5**.

The first step of the surprising conversion **1** → **5** is evidently a nucleophilic substitution with allyl rearrangement (S_N2' reaction) to give an intermediate, which is successively substituted by methoxide ions to give **2**. Orthoesters **2** and esters **5** can be purified by 'Kugelrohr' distillation; the carboxylic acids **3** are accessible from **5** by alkaline hydrolysis (*e.g.* **1a** → **3a**, 74%, without isolation of **5a**).

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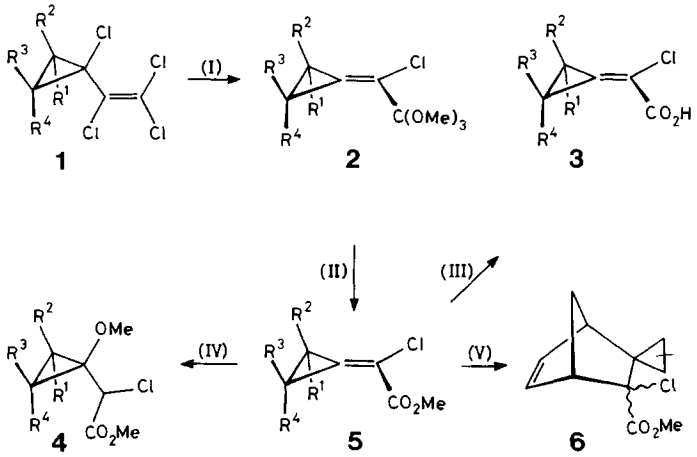

(I): MeOH/KOH (3:1); (II): $H^{\oplus}$, H_2O, RT; (III): $OH^{\ominus}$, H_2O/EtOH, RT; (IV): MeOH; (V): cyclopentadiene, 80 °C.

Table 1. Orthoesters **2** and esters **5** from cyclopropanes **1**.

	R^1	R^2	R^3	R^4	*t* [h]	Yield [%] **2**	**5**
a	CH_3	CH_3	CH_3	CH_3	8	65	87
b	H	—$(CH_2)_4$—		H	8	24 [a]	94
c	CH_3	H	H	CH_3	6	51	98
d	CH_3	H	CH_3	H	6	59	92
e	C_2H_5	H	H	H	4	55	95
f	CH_3	H	H	H	4	49	95
g	H	H	H	H	4	60	94

[a] After gas-chromatographic isolation.

The cyclopropylidene acetic acid esters **5** are versatile ring strain-activated acrylic esters. In particular the unsubstituted compound **5g**, a chlorinated cyclic analogue of the senecionic acid ester, exhibits its excellent reactivity in cycloadditions and as Michael acceptor[4]. On heating, it undergoes [2+2]-cyclodimerization to the dichlorodispiro-[2.0.2.2]octanedicarboxylate; on heating with 1,3-dienes it affords the Diels-Alder adducts (*e.g.* with cyclopentadiene **6g**, 91%), and with methanol it forms the Michael adduct **4g** already at room temperature.

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1a, 72866-04-7; **1b**, 80631-29-4; **1c**, 83024-16-2; **1d**, 80695-56-3; **1e**, 82979-25-7; **1f**, 82979-26-8; **1g**, 82979-27-9; **2a**, 82979-28-0; **2b**, 82979-29-1; **2c**, 82979-30-4; **2d**, 82979-31-5; **2e**, 82979-32-6; **2f**, 82979-33-7; **2g**, 82979-34-8; **3a**, 82979-37-1; **4a**, 82979-36-0; **5a**, 82979-39-3; **5b**, 82979-40-6; **5c**, 82979-41-7; **5d**, 82979-42-8; **5e**, 82979-43-9; **5f**, 82979-44-0; **5g**, 82979-45-1; **6f**, 82979-38-2; **6g** isomer 1, 82979-35-9; **6g** isomer 2, 83024-17-3; cyclopentadiene 542-92-7

[1] Cf. A. de Meijere, *Angew. Chem. 91* (1979) 867; *Angew. Chem. Int. Ed. Engl. 18* (1979) 809, and references cited therein.
[2] W. Weber, A. de Meijere, *Angew. Chem. 92* (1980) 135; *Angew. Chem. Int. Ed. Engl. 19* (1980) 138.
[3] Th. Liese, G. Splettstösser, A. de Meijere, *Tetrahedron Lett. 1982*, in press.
[4] Cf. D. Spitzner, A. Engler, Th. Liese, G. Splettstösser, A. de Meijere, *Angew. Chem. 94* (1982) 799; *Angew. Chem. Int. Ed. Engl. 21* (1982) 791.

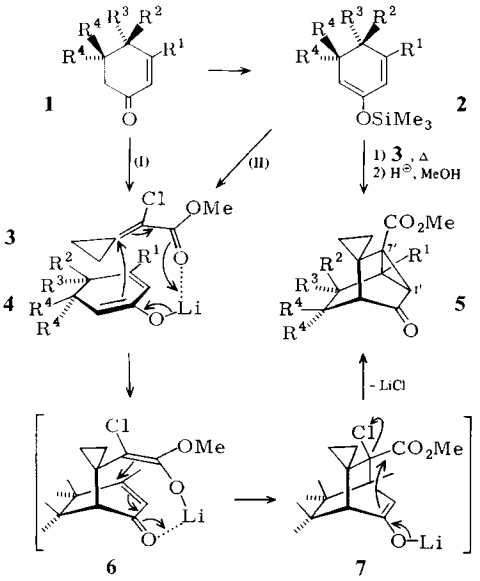
Reactivity by Ring Strain: Spirocyclopropyl-Annelated Tricyclic Skeletons by a One-Pot Three-Step Reaction**

By *Dietrich Spitzner**, *Anita Engler*, *Thomas Liese*, *Gisela Splettstösser*, and *Armin de Meijere**

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

The modified acrylic acid ester methyl 2-chloro-2-cyclopropylidene acetate **3**[1] owes its enhanced reactivity in cycloadditions and towards nucleophiles[1] to the electronic effects of ring strain. Aside from its utility as a dienophile, **3** is a particularly useful building block in Michael[2] and tandem Michael reactions.

In analogy to other acrylic acid esters[3,4] **3** reacts with lithium cyclohexadienolates **4**—prepared from the corresponding cyclohexenones **1** and lithium diisopropylamide or from the enoltrimethylsilyl ethers **2** and butyllithium—in the sense of a double Michael reaction to give the enolates of the oxobicyclo[2.2.2]octane-*endo*-carboxylic esters **7**, which spontaneously cyclize with loss of chloride to give the tricyclo[3.2.1.$0^{2,7}$]octane derivatives **5**[4] (see Table 1). The same products are also formed, along with others,



(I): LDA, THF, −60 °C; (II): *n*BuLi, THF/*n*-Hexane, −60 °C.

Table 1. 8′-Oxospiro[cyclopropane-1,6′-tricyclo[3.2.1.$0^{2,7}$]octane]-7′-carboxylic acid methyl esters **5** from **3** and lithium cyclohexadienolates **4**.

	R^1	R^2	R^3	R^4	Yield [%] [a]	
a	CH_3	H	H	H	64 [b]	A, B
b	H	CH_3	CH_3	H	52	B
c	CH_3	H	H	CH_3	75	B
d	H	H	H	H	20	B
e	—$(CH_2)_2$—CH(OBu^t)— [c]		CH_3	H	79 [d]	A

[a] Isolation: A: recrystallization; B: Kugelrohr distillation. [b] M.p. 91–92 °C. [c] Enolate from (1*S*,7a*S*)-1-*tert*-butoxy-7a-methyl-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-one. [d] M.p. 132 °C, $[\alpha]_D^{25} = +111$ ($c = 0.4$, EtOH).

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in the purely thermal Diels-Alder reaction of **3** with **2** and subsequent acid (hydrochloric acid/methanol) work-up, albeit in substantially poorer yields (*e.g.* **5a** from **2a**: 29%).

Products of type **5** are formed from **4** and **3** in distinctly higher yields than from **4** and α-bromocrotonates[4]. This can only be explained in terms of **3** being preoriented above the dienolate **4** with the lithium ion's assistance in the initial step of the three-step reaction and therefore in the second step predominantly **7** being formed with *anti*-chloro substituents, so that cyclization to **5** can take place by rear-side nucleophilic attack.

The three-membered ring in the skeleton of **5** can be reductively opened between $C^{1'}$ and $C^{7'}$ with lithium in liquid ammonia. If one further takes into account that, as a rule, a spirocyclopropyl is hydrogenated to a *gem*-dimethyl group[5], then this reaction sequence with **3** opens an entry to certain terpene skeletons, which are not obtainable with the far less reactive 3,3-dimethylacrylic acid esters (senecionic esters). For example, **5e** is a precursor of the diterpene eremolactone.

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CAS Registry numbers:
1a, 1193-18-6; **1b**, 1073-13-8; **1c**, 78-59-1; **1d**, 930-68-7; **1e**, 41878-38-0; **2a**, 54781-27-0; **2b**, 54781-30-5; **2c**, 54781-28-1; **2d**, 54781-19-0; **2e**, 83057-76-5; **3**, 82979-45-1; **4a**, 82995-19-5; **4b**, 82995-20-8; **4c**, 76639-03-7; **4d**, 76639-02-6; **4e**, 82995-21-9; **5a**, 82995-22-0; **5b**, 82995-23-1; **5c**, 82995-24-2; **5d**, 82995-25-3; **5e**, 82995-26-4

[1] Th. Liese, G. Splettstösser, A. de Meijere, *Angew. Chem. 94* (1982) 799; *Angew. Chem. Int. Ed. Engl. 21* (1982) 790.
[2] Cf. N. F. Osborne, UK Pat. Appl. 2049660 (Cl C 07D499/82); *Chem. Abstr. 95* (1981) 62190g.
[3] R. A. Lee, *Tetrahedron Lett. 1973*, 3333.
[4] Cf. H. Hagiwara, T. Kodama, H. Kosugi, H. Uda, *J. Chem. Soc. Chem. Commun. 1976*, 413.
[5] C. Gröger, H. Musso, *Angew. Chem. 88* (1976) 415; *Angew. Chem. Int. Ed. Engl. 15* (1976) 373; and references cited therein.

Generation and NMR-Detection of the Anions *N*-Methyl-1-benzazocinide, 1-Benzazocindiide, and Dibenz[*b*,*g*]azocindiide; A Family of Aromatic π-Excessive Compounds**

By *A. G. Anastassiou**, *H. S. Kasmai* and *D. Hauger*

In recent reports we recorded and interpreted information based on direct ^{1}H- and ^{13}C-NMR observation of certain novel π-excessive heterocyclic anions **1**[1a,d], **2**[1c] and **3**[1b] which led, rather surprisingly, to the classification of the "4n"-electron, potentially antiaromatic, π-excessives **1** and **2** as extensively delocalized and strongly paratropic, and the "4n + 2" counterpart **3** as largely localized and distinctly atropic. Further, having reasoned that the failure of **3** to realize its aromatic potential could be due, at least in large measure, to a skeletally-induced resistance of the central ring toward adopting the required planar geometry

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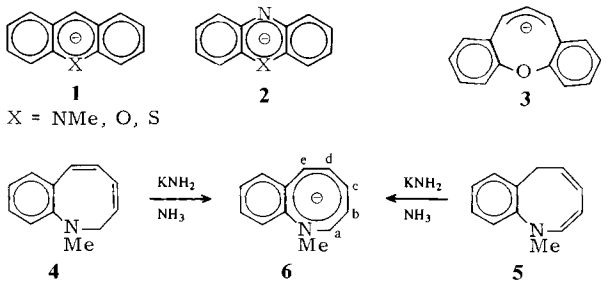
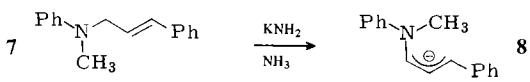
we resolved to examine a monobenzo member of the family along similar lines. To this end, we chose the *N*-methyl benzazocinide shown in **6**, which we readily prepared on exposure of either of the two known cyclic anilines **4**[2] and **5**[2] to KNH_2 in liquid ammonia at *ca.* −30 °C.



1 **2** **3** **4** **6** **5**

Suitable analysis of the highly resolved ^{1}H-NMR spectrum of **6** reproduced in Figure 1a afforded the listed assignments and coupling constants, the latter being associated with a magnitude and uniformity normally reserved for π rings which are both flat (or very nearly so) and extensively delocalized. Further, comparison of the two key ^{1}H-NMR doublets of **6** ($\delta = 5.00$ and 5.62) with those of model anion **8** ($\delta = 3.92$ and 4.46) reveals a substantial



downfield shift of the former in relation to the latter, a fact which allows one to deduce that benzazocinide **6** is detectably diatropic. Equally implicative of the enhanced π mobility of the heteroatomic lone pair of **6** compared to that of the model **8** are the ^{1}H- and ^{13}C-NMR downfield shifts of the methyl appendages one observes on passing from **8** (δ, 3.15 and 38.14 ppm) to **6** (δ, 3.55 and 46.59 ppm).

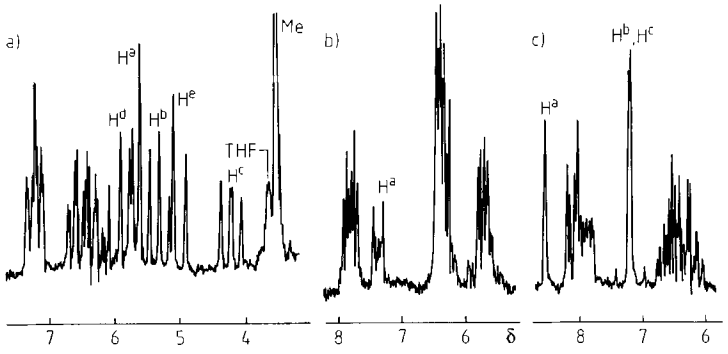
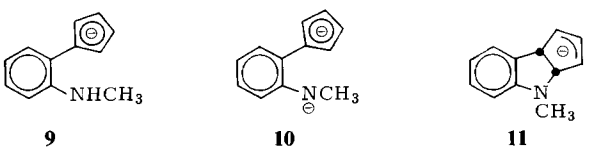


Fig. 1. 60 MHz-^{1}H-NMR spectra of the potassium salt of a) **6**, b) **13** and c) **15** in liquid NH_3 at *ca.* 34 °C with THF as internal standard. Coupling constants of **6**: $J_{a,b} = J_{b,c} = 8.5$; $J_{c,d} = 10.5$, $J_{d,e} = 11.0$ Hz.

From a chemical viewpoint it is significant to note that despite its diatropic character, the eight-membered moiety of **6** is *not* thermally stable, cleanly rearranging ($t_{1/2} \approx 522$ min) to produce the two component mixture of monoanion **9** and dianion **10** [$\delta(^{13}C)Me = 39.10$ and 17.88, respectively] upon mild heating (34.9 °C); this reorganization is quite likely intermediated by the benzobicycle **11**[3].



9 **10** **11**

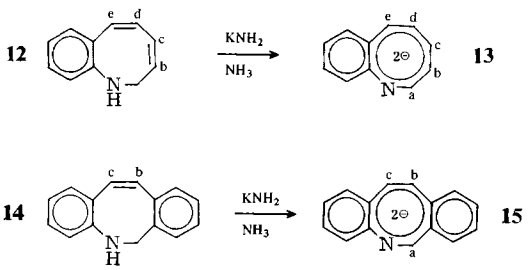
Furthermore, the related dianion **13** and the linearly fused dibenzo counterpart **15** were readily prepared upon exposure of annelated anilines **12** and **14** to an excess of KNH_2 in liq. NH_3 at *ca.* −35 °C. In turn, **12** and **14** were prepared by reduction of the corresponding lactams with $LiAlH_4$[2].

The well resolved ^{1}H-NMR spectra of **13** and **15**, reproduced in Figures 1b and 1c, respectively, are clearly indicative of frames which are endowed with a substantial degree of diatropic π mobility. Particularly revealing in this connection are, of course, (*i*) the distinctly low field resonance due to H^a of **15** (singlet at $\delta = 8.35$) and (*ii*) the low field position ($\delta = 7.4$) and relatively large coupling constant (9.5 Hz) of the H^a doublet in the spectrum of **13**; further, the ^{13}C-NMR characteristics of **13** and **15** are strongly implicative of the key geometric constraint imposed by π mobility, namely planarization of the molecule's eight-membered moiety. Specifically, one notes upon comparing the relatively strain-free, heavily buckled, eight-membered frames of **12** and **14** to those of dianions **13** and **15** in terms of C—H coupling constants (Table 1) that these uniformly become significantly smaller (10 to 25 Hz) on passing to the dianion. And bearing in mind that below-average C—H coupling constants associated with a medium-large π periphery are normally indicative of molecular flattening[1b,4] we interpret the data collected in Table 1 to

Table 1. ^{13}C-NMR data of C^b to C^e in **12** and **13** and of C^b and C^c in **14** and **15** in liquid NH_3 at *ca.* 34 °C, [D_8]tetrahydrofuran as internal standard. The δ values (referred to TMS) have not been assigned.

	12	13	14	15
δ	118.30	87.43	116.70	97.46
	120.49	91.14	118.15	102.80
	126.09	93.71		
	128.57	101.63		
$J_{C,H}$	162	146	164	140
[Hz]	157	142	154	147
	≈165	141		
	158	140		

mean that the formation of "4n+2" dianions **13** and **15** is attended by a significant degree of planarization. Also, the rather substantial upfield shift (14—30 ppm) experienced by the carbon centers of the eight-membered rings of **13** (C^b to C^e) and **15** (C^b, C^c) relative to their counterparts in **12** and **14** is fully consistent with the presence of substantial charge delocalization in the dianions.



The monoanions **6** and **9** and the dianion **13** gave the products to be expected, after quenching with water and hydrogenation; **15** was converted into **14** upon exposure to moist ether.

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6, 83095-36-7; **9**, 83077-01-4; **10**, 83077-02-5; **13**, 83077-03-6; **15**, 83077-04-7

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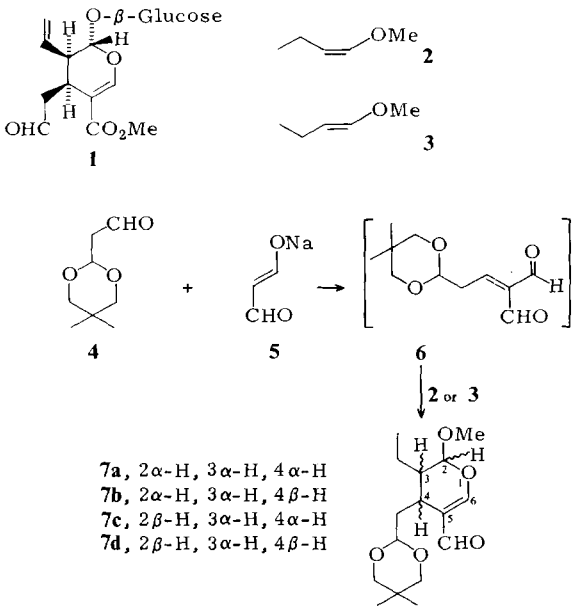
[1] a) A. G. Anastassiou, H. S. Kasmai, *Angew. Chem. 92* (1980) 53; *Angew. Chem. Int. Ed. Engl. 19* (1980) 43; b) *ibid. 92* (1980) 402 and *19* (1980) 393; c) A. G. Anastassiou, H. S. Kasmai, M. R. Saadein, *ibid. 93* (1981) 111 bzw. *20* (1981) 115; d) *Tetrahedron Lett. 21* (1980) 3743.
[2] R. M. Coates, E. F. Johnson, *J. Am. Chem. Soc. 93* (1971) 4016.
[3] It is pertinent to note in this connection that while the rearrangement of **6** to **9** and **10** was not previously reported, the grater kinetic acidity of **4** and **5** relative to that of appropriate models was suitably attributed to "a small degree of aromatic stabilization in the incipient 10π electron anion" *i.e.*, **6** [2].
[4] A. G. Anastassiou, E. Reichmanis, *J. Am. Chem. Soc. 98* (1976) 8366.

A Simple and Stereoselective Entry to the Secoiridoids by [4+2]-Cycloaddition of Alkylidene-1,3-dicarbonyl Compounds**

By *Lutz-F. Tietze*, Karl-Heinz Glüsenkamp,* and *Wolfgang Holla*

Secologanin **1**, a key-compound in the biosynthesis of numerous alkaloids[1], belongs to the secoiridoids, a widely occurring class of natural products derived biogenetically from geraniol. The synthesis of compounds of the secologanin type[2] is difficult because of the polyfunctionality, high reactivity, and the stereochemical requirements. We have now succeeded in obtaining the C_{10}-system in a one-pot synthesis from one C_4-moiety and two C_3-moieties; the crucial step is a [4+2]-cycloaddition with inverse electron demand.



7a, 2α-H, 3α-H, 4α-H
7b, 2α-H, 3α-H, 4β-H
7c, 2β-H, 3α-H, 4α-H
7d, 2β-H, 3α-H, 4β-H

When an aqueous solution of the sodium salt of malonic dialdehyde **5** is allowed to react with the monoacetal **4**[3] for 48 h at 5 °C and the reaction mixture is subsequently treated with (*Z*)- or (*E*)-1-methoxy-1-butene **2**, or **3** and sodium dihydrogen phosphate, **7** is formed directly; the reaction initially leads *via* the aldol adduct to the alkylidene compound **6**, which spontaneously reacts further with the enol ethers to give the cycloadducts. **2** affords 64% of a *ca.* 1:1 mixture of the two isomers **7a** and **7b**, while **3** furnishes 48% of the secologanin derivative **7c**, which at all chiral centers has the relative configuration typical for the secoiridoids[4]. 16% of the undesired stereoisomer **7d** is also formed; however, this can be separated chromatographically.

The high rate of reaction of the [4+2]-cycloaddition is due to the fact that the energy of the LUMO, and thus also the free activation enthalpy of the reaction, is considerably lowered by the electron acceptor group on the heterodiene. Similar results have also been obtained with other alkylidene-1,3-dicarbonyl compounds[5]. This simple entry to the secoiridoids is capable of wide variation by use of substituted C_3- and C_4-moieties.

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CAS Registry numbers:
2, 10034-12-5; **3**, 10034-13-6; **4**, 82995-27-5; **5**, 82995-28-6; **7a**, 82995-29-7; **7b**, 82995-30-0; **7c**, 82995-31-1; **7d**, 82995-32-2

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

[1] G. A. Cordell, *Lloydia 37* (1974) 219; H. Inouye, *Planta Med. 33* (1978) 193; A. R. Battersby, M. Thompson, K.-H. Glüsenkamp, L.-F. Tietze, *Chem. Ber. 114* (1981) 3430; A. R. Battersby, N. D. Westcott, K.-H. Glüsenkamp, L.-F. Tietze, ibid. 114 (1981) 3439; J. Stöckigt, in J. D. Phillipson, M. H. Zenk: *Indole and Biogenetically Related Alkaloids*, Academic Press, London 1980, p. 113.
[2] L.-F. Tietze, *J. Am. Chem. Soc. 96* (1974) 946; G. Kinast, L.-F. Tietze, *Chem. Ber. 109* (1976) 3626; L.-F. Tietze, G. Kinast, H. C. Uzar, *Angew. Chem. 91* (1979) 576; *Angew. Chem. Int. Ed. Engl. 18* (1979) 541; cf. also C. R. Hutchinson, K. C. Mattes, M. Nakane, J. J. Partridge, M. R. Uskokovic, *Helv. Chim. Acta 61* (1978) 1221; M. Nakane, C. R. Hutchinson, *J. Org. Chem. 45* (1980) 4233.
[3] **4** is obtained by reaction of 1,1,3,3-tetramethoxypropane with 2,2-dimethyl-1,3-propanediol (1:1, 140 °C, catalytic amounts of H_2SO_4; b.p. 87–92 °C/8 torr) and subsequent hydrolysis (1,2-dichloroethane/tetrahydrofuran, silica gel, oxalic acid, 60 °C; b.p. 84 °C/8 torr); yield 55%.
[4] The monohydrate of **5** (168 mg, 1.30 mmol) is added to a solution of **4** (158 mg, 1.00 mmol) in oxygen-free water (2.0 mL) and the mixture stirred for 48 h at 5 °C and finally warmed to room temperature. It is then treated with 300 mg (3.49 mmol) of enol ether **2** or **3** (dissolved in 3 mL of 1,2-dichlorethane) and, with vigorous stirring, portionwise with 600 mg (3.85 mmol) of sodium dihydrogen phosphate · $2H_2O$. After 2 h, 500 mg of sodium hydrogen carbonate is added, the mixture diluted with water, and then extracted with chloroform. After washing, drying and evaporating, the concentrated extract is chromatographed on silica gel with ether/petroleum ether (1:2): $R_F = 0.10$; ^{1}H-NMR ($CDCl_3$): $\delta = 0.70$ (s, 3H, CH_3), 0.97 (t, $J = 7.5$ Hz, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.28–1.74 (m, 4H, CH), 1.86 (m, 1H, CH), 2.97 (m, 1H, 4-H), 3.20–3.68 (m, 4H, CH_2O), 3.58 (s, 3H, OCH_3), 4.50 (t, $J = 5$ Hz, 1H, O—CH—O), 4.90 (d, $J = 8.5$ Hz, 1H, 2-H), 7.23 (s, 1H, 6-H), 9.25 (s, 1H, CHO). **7d**: $R_F = 0.13$; ^{1}H-NMR ($CDCl_3$): $\delta = 0.70$ (s, 3H, CH_3), 0.94 (t, $J = 7.0$ Hz, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.08–1.40 (m, 2H, aliph.-H), 2.04 (mc, 3H, aliph.-H), 2.64 (t, br, $J = 7$ Hz, 1H, 4-H), 3.52 (mc, 4H, CH_2O), 3.48 (s, 3H, OCH_3), 4.60 (t, $J = 5$ Hz, 1H, O—CH—O), 5.00 (t, $J = 1$ Hz, 1H, 2-H), 7.18 (s, 1H, 6-H), 9.36 (s, 1H, CHO). The assignment of **7c** and **7d** was accomplished, *inter alia*, by comparison of the ^{1}H-NMR spectra with those of secologanin derivatives. L.-F. Tietze, S. Henke, *Angew. Chem. 93* (1981) 1005; *Angew. Chem. Int. Ed. Engl. 20* (1981) 970; cf. also J. R. Purdy, R. G. Hamilton, L. Akhter, S. McLean, *Can. J. Chem. 59* (1981) 210.
[5] L.-F. Tietze, G. von Kiedrowski, K. Harms, W. Clegg, G. Sheldrick, *Angew. Chem. 92* (1980) 130; *Angew. Chem. Int. Ed. Engl. 19* (1980) 134; L.-F. Tietze, G. von Kiedrowski, *Tetrahedron Lett. 22* (1981) 219; L.-F. Tietze, K.-H. Glüsenkamp, K. Harms, G. Remberg, G. M. Sheldrick, *ibid. 23* (1982) 1147; L.-F. Tietze, G. von Kiedrowski, B. Berger, *Angew. Chem. 94* (1982) 222; *Angew. Chem. Int. Ed. Engl. 21* (1982) 221; J. Bitter, J. Leitich, H. Partale, O. E. Polansky, W. Riemer, U. Ritter-Thomas, B. Schlamann, B. Stilkerieg, *Chem. Ber. 113* (1980) 1020; B. B. Snider, *Tetrahedron Lett. 21* (1980) 1133; B. B. Snider, D. M. Roush, T. A. Killinger, *J. Am. Chem. Soc. 101* (1979) 6023; R. R. Schmidt, M. Maier, *Tetrahedron Lett. 23* (1982) 1789; C. Reichardt, K.-Y. Yun, *ibid. 23* (1982) 3163.

Synthesis of S_{11} and S_{13}**

By *Torsten Sandow, Jürgen Steidel,* and *Ralf Steudel**

Sulfur homocycles are synthesized from chlorosulfanes in accordance with eq. (a)[1]. Thus, S_7 can be prepared from S_2Cl_2, and S_9 from S_4Cl_2. Larger rings S_n ($n = 11, 13, \ldots$) were hitherto not accessible in this way, since the corresponding chlorosulfanes could either not be prepared or, if at all, only with difficulty and in insufficient purity[2].

$$(C_5H_5)_2TiS_5 + S_mCl_2 \xrightarrow[0\,^\circ C]{CS_2} (C_5H_5)_2TiCl_2 + S_{m+5} \quad (a)$$

$$S_n + Cl_2 \xrightarrow[20\,^\circ C]{CS_2/CCl_4} S_nCl_2\ (n = 6, 8) \quad (b)$$

We have now synthesized S_6Cl_2 and S_8Cl_2 from the elements according to eq. (b)[3a], and then—analogously to the synthesis of S_7[3b]—prepared S_{11} and S_{13} according to eq. (a)[4]. An excess of sulfur (S_6 and S_8, respectively) is used in the chlorination, and unreacted sulfur is subsequently removed from the reaction mixture by evaporation, cooling, and crystallization. The mixture of cyclic sulfurs formed during the synthesis of S_{11} and S_{13} is partially precipitated as oil, S_{11} and S_{13} remaining dissolved in the mother liquor and only crystallizing out on further concentration and cooling[4]. After twofold recrystallization from $CHCl_3$, 7% of pure S_{11} and 5% of pure S_{13} were obtained; the identity and purity of the two sulfur rings were determined by HPLC[5]. S_{11} and S_{13} have previously been detected in rapidly cooled liquid sulfur and in other sulfur preparations[5].

S_{11} (m.p. 74 °C, dec.) forms rod-shaped crystals which grow in bundles; S_{13} (m.p. 114 °C, dec.) crystallizes in clear well-formed hexagonal platelets. Both species are readily soluble in CS_2 and moderately soluble in CCl_4, $CHCl_3$, CH_2Cl_2 and toluene. The EI mass spectra (70 eV; sample temperature up to 160 °C) show only fragment ions $S_n^{\oplus}$ ($n = 1-9$); the Raman spectra (Table 1) are different from those of all other known sulfur modifications[5]. Both species are about as thermally stable as S_6, which can be handled without decomposition for hours at room temperature.

Table 1. Raman spectra of crystalline cycloundecasulfur (S_{11}) and cyclotridecasulfur (S_{13}) at −100 °C ($Kr^{\oplus}$ laser, spectral slit width 3 cm^{-1}, wave numbers in cm^{-1}, rel. intensities in brackets, b broad, sh shoulder).

S_{11}	S_{13}
ν_{SS}: 480 (19), 464 (87), 442 (6, b), 411 (16)	ν_{SS}: 497 (11), 480 (15), 461 (100), 440 (19), 413 (9), 386 (13, b)
286 (3), 266 (2, b), 248 (3), 221 (13), 201 (4), 178 (52), 169 (35), 132 (19), 110 (sh), 102 (7), 85 (sh), 71 (100), 53 (76), 42 (30), 33 (20)	281 (15), 263 (3), 246 (7), 222 (4), 202 (19), 191 (14), 174 (32), 162 (8), 136 (37), 122 (3), 102 (31)

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S_{11}, 60349-28-2; S_{13}, 77152-68-2; S_6Cl_2, 35000-36-3; S_8Cl_2, 12182-73-9; $(C_5H_5)_2TiS_5$, 12116-82-4.

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[**] Sulfur Compounds, Part 80. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 79: R. Steudel, R. Strauss, *Z. Naturforsch. B*, in press.

[1] Cf. M. Schmidt, *Angew. Chem. 95* (1973) 474; *Angew. Chem. Int. Ed. Engl. 12* (1973) 445. The preparation of S_{11} according to eq. (a) is mentioned therein, but so far no details of the synthesis nor of the properties of the compound have been published.

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[3] Pure S_7Cl_2 can be obtained analogously from S_7 (R. Steudel, H.-J. Mäusle, unpublished); b) M. Schmidt, B. Block, H.-D. Block, H. Köpf, E. Wilhelm, *Angew. Chem. 80* (1968) 660; *Angew. Chem. Int. Ed. Engl. 7* (1968) 632.

[4] Procedure for S_{11} (in brackets for S_{13}): A stirred solution of 90 g S_6 in 1.3 L CS_2 (160 g S_8 in 0.6 L CS_2) is treated dropwise at 0 °C with 100 mL (200 mL) of a saturated solution of Cl_2 in CCl_4 (*ca.* 4%), warmed to 20 °C, stirred for 1 h (3 h), evaporated down to 100 mL in a vacuum, and, after filtration, freed of solvent in a vacuum. The oil thus obtained is allowed to stand for 3 d at −35 °C and pipetted from the solid residue (S_6 or S_8). Yield: 15 g S_6Cl_2 (31 g S_8Cl_2).—A solution of 5 g $(C_5H_5)_2TiS_5$ in 80 mL CS_2 is treated within 30 min at 0 °C with a solution of 4 g S_6Cl_2 (4.8 g S_8Cl_2) in 20 mL CS_2; after 3 h (2 h) the mixture is filtered.—S_{11}: After addition of 50 mL $CHCl_3$, evaporation to 50 mL, addition of a further 100 mL $CHCl_3$ and decantation from the separated oil, the remaining solution is cooled to −35 °C for 24 h. The crystallizate (0.9 g) is recrystallized twice from $CHCl_3$. Yield 0.36 g S_{11}.—S_{13}: After addition of 40 mL $CHCl_3$, filtration, addition of a further 70 mL $CHCl_3$ and cooling to −35 °C (5 d), 1.56 g of crude product crystallizes. Yield after twofold recrystallization from $CHCl_3$: 0.29 g S_{13}.

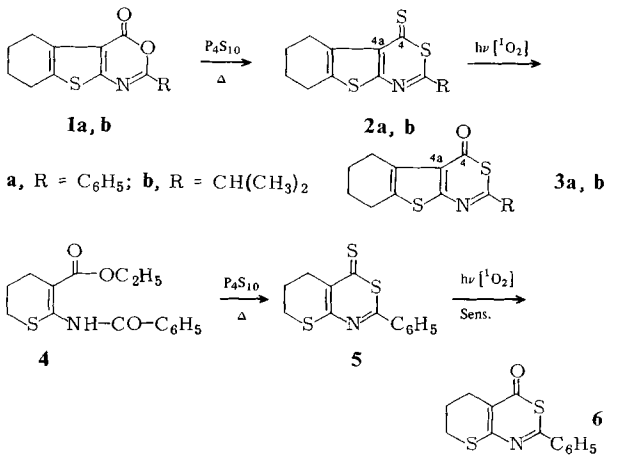
[5] R. Steudel, H.-J. Mäusle, D. Rosenbauer, H. Möckel, T. Freyholdt, *Angew. Chem. 93* (1981) 402; *Angew. Chem. Int. Ed. Engl. 20* (1981) 394; R. Steudel, *Top. Curr. Chem. 102* (1982) 149.

Selective Sulfuration and Photooxidation of Heteroannelated 1,3-Oxazin-6-ones to 1,3-Thiazin-6-ones**

By *Heinrich Wamhoff** and *Mümtaz Ertas*

In memoriam Burckhardt Helferich

The heteroannelated 1,3-oxazin-6-ones **1a**, **b**[2], obtained by treatment of acylated enamino esters with Ph_3PCl_2, and



Sens. = methylene blue; hν: $\lambda > 313$ nm, solvent: benzene; high-pressure mercury lamp HPK 125 W

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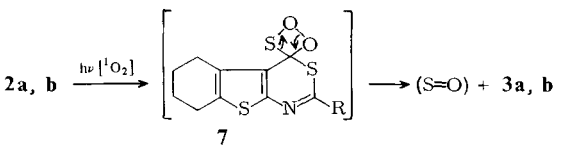
the ethyl 6-benzoylamino-3,4-dihydro-2*H*-thiopyran-5-carboxylate **4** are sulfurated to the novel deep-red 1,3-thiazin-6-thiones **2a**, **b** and **5**, respectively, on treatment with P_4S_{10} in boiling xylene[3]. **2a**: 83%, m.p. 200 °C; **2b**: 78%, m.p. 82 °C; **5**: 65%, m.p. 102 °C[4].

2a, b and **5** are converted rapidly, selectively and almost quantitatively into 1,3-thiazin-6-ones **3a**, **b** and **6**, respectively, by long-wave UV irradiation in the presence of oxygen. For example, a solution of **2a**, **b** (10 mmol) in benzene (200 mL) is irradiated (Pyrex filter) until the color changes from red to yellow (*ca.* 2—3 h) while oxygen is passed through the solution. The 5,6,7,8-tetrahydro-4*H*-[1]benzothieno[2,3-*d*][1,3]thiazin-4-ones **3a**, **b** are isolated after removal of the solvent (**3a**: 97%, m.p. 160 °C; **3b**: 95%, m.p. 133 °C[4]). In the case of **5** addition of methylene blue as sensitizer is necessary; after 4 h, **6** (92%, m.p. 124 °C[4]) is obtained by chromatography of the residue.

The oxidative photodesulfurization of heterocyclic thiones has only scarcely been described in the literature[5]. Hereby a cycloaddition of singlet oxygen to the CS double bond with subsequent (SO)-extrusion from the 1,2,3-dioxathietane **7** is discussed.



7

2a, **b** act simultaneously as sensitizers (**2a**: λ_{max} [nm] (lgε) 450, 344, 302 (3.73, 4.00, 3.97); **2b**: 425, 323 (3.63, 3.99)), whereas the UV excitation of **5** (395, 325 (3.84, 4.09)) is apparently not sufficient for the oxygen sensitization, which requires addition of methylene blue.

Characteristic in the broad-band decoupled ^{13}C-NMR spectrum of **2b** are the signals of thiocarbonyl C-4 (**2b**: $\delta = 200.10$; for comparison, **3b**: 177.68) and the neighboring C-4a (**2b**: $\delta = 130.10$; for comparison **3b**: 119.84).

This combination of a sulfuration and a photooxidation step represents a simple and elegant method for the synthesis of heteroannelated 1,3-thiazin-6-ones, which in turn can be used widely for the synthesis of heterocycles.

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1a, 73696-35-2; **1b**, 79750-94-0; **2a**, 63274-56-6; **2b**, 63274-55-5; **3a**, 63274-59-9; **3b**, 83135-75-5; **4**, 79750-89-3; **5**, 83135-76-6; **6**, 83135-77-7

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[2] D. Achakzi, M. Ertas, R. Appel, H. Wamhoff, *Chem. Ber. 114* (1981) 3188; H. Wamhoff, G. Hendrikx, M. Ertas, *Liebigs Ann. Chem. 1982*, 489.

[3] L. Legrand, *Bull. Soc. Chim. Fr. 1960*, 337; L. Legrand, N. Lozac'h, *ibid. 1967*, 2067.

[4] All compounds gave correct elemental analyses and spectroscopic data. IR: νCO, νCN = 1650, 1550 (**3a**), 1660, 1540 (**3b**); 1630, 1530 cm^{-1} (**6**). MS: m/z (M^+) = 299 (**3a**); 265 (**3b**); 261 (**6**).

[5] A. Schönberg, A. Mustafa, *J. Chem. Soc. 1943*, 275; N. Ishibe, M. Odani, M. Sunami, *Chem. Commun. 1971*, 118; N. Suzuki, K. Sano, N. Tani, Y. Izawa, *Heterocycles (Sendai) 16* (1981) 1133.

$[Mo_4^{III}S_4(CN)_{12}]^{8-}$, a Cluster with High Negative Charge and Cubane-Like Mo_4S_4-Moiety—On the Significance of Cyanothiomolybdates for the Prebiotic Evolution

By *Achim Müller**, *Werner Eltzner*, *Hartmut Bögge*, and *Rainer Jostes*

The occurrence of CN^-, S^{2-} and Precambrian Mo-S-phases on primordial earth suggests that cyanothiomolybdates could have been of importance for the evolution of Mo-enzymes (which were active at a very early stage in the phylogenesis of the prokaryotes through their presence in the oldest anaerobic organisms)[1-3]. We have found that in the system $Mo^{n+}/S^{2-}/CN^-$ cyanothiomolybdates with central di-, tri- and tetranuclear cluster moieties are formed, which, *inter alia*, compare with those in ferredoxins and exhibit properties which are relevant to the above mentioned subject of our studies. A typical example is $K_8[Mo_4S_4(CN)_{12}]\cdot 4H_2O$ **1**, generated by reaction of MoS_3 with aqueous CN^- solution, which could be isolated pure, and characterized by elemental analysis, TG/DTA, magnetic measurements, MO calculations, IR, Raman, NIR/VIS/UV and XPE spectroscopy, as well as by a complete single-crystal structure analysis.

The new compound **1** contains the remarkable eightfold negatively charged $[Mo_4S_4(CN)_{12}]^{8-}$ anion **2** (Fig. 1). The overall crystallographic symmetry of **2** is $\bar{4}2m$ (D_{2d}), the idealized $\bar{4}3m$ (T_d). The central cluster moiety is a distorted cube [Mo—S: 238.2(2), 238.1(2) pm (2×)]. The Mo and S atoms each form an almost regular tetrahedron [Mo—Mo: 285.5(1), 285.3(1) (2×); S—S: 375.5(3), 376.0(3) pm (2×)]. Each Mo is octahedrally surrounded by three CN^- and three S^{2-} [Mo—C: 219.0(10), 219.1(8) pm (2×)].

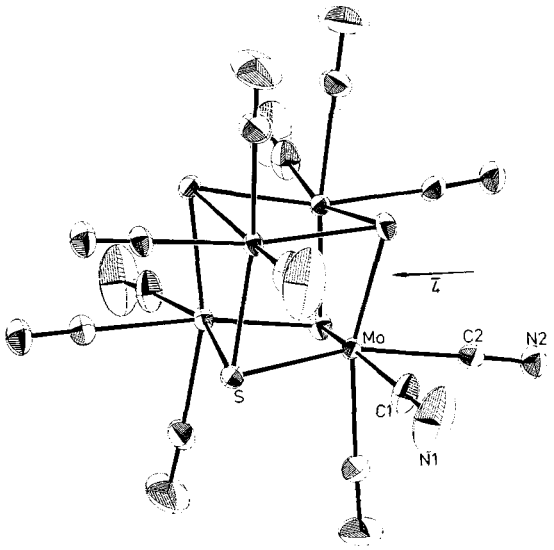

Fig. 1. Structure of **2** in crystals of **1** (space group $P4_2/nmc$, $a = b = 1236.1(5)$, $c = 1163.6(5)$ pm, $Z = 2$; $R = 0.051$ (880 observed reflections).

In **2** there are strong Mo—Mo interactions, since **1** is diamagnetic. Similar metal-metal distances are found in Mo-clusters with single bonds.

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The ESCA bond energies [E_B(Mo-3p$_{3/2}$) = 395.1, E_B(Mo-3d$_{5/2}$) = 229.0 eV rel. E_B(C-1s$_{1/2}$) = 285.0 eV] are consistent with values expected for $Mo^{III}(d^3)$. According to a simple cluster rule, for this electron configuration a metal tetrahedron is to be expected, however, in contrast to the metal triangle (for d^2), this has seldom been found.

So far the following cyanothiomolybdates have been isolated: $[(CN)_4MoS_2Mo(CN)_4]^{6-}$, $[(CN)_4MoS_2Mo(CN)_4]^{4-}$, $[(CN)_6MoSMo(CN)_6]^{6-}$, and $[(Mo_3S_4(CN)_9]^{5-}$, which is also formed in the above mentioned reaction (the skeleton can formally be derived by removal of an $Mo(CN)_3$ corner from **2**)[8, 14, 17]. A significant observation is that complexes with various electron populations exist and, according to ESCA data, exhibit a large variation in bonding energy of the S-2p electrons (and thus can act as electron reservoirs).

The following steps seem plausible for the evolution of the Mo-enzymes: $MoS_x + CN^-$ ("solution process") → cyanothiomolybdates → Mo complexes with simple S-containing ligands (amino acids) → "early" enzymes.

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The complete manuscript of this communication appears in: *Angew. Chem. Suppl. 1982*, 1643-1661

[1] H. Follmann: *Chemie und Biochemie der Evolution*. Quelle and Meyer, Heidelberg 1981.
[2] M. T. Beck, J. Ling, *Naturwissenschaften 64* (1977) 91; cf. M. T. Beck "Prebiotic Coordination Chemistry: The Possible Role of Transition Metal Complexes in the Chemical Evolution" in H. Sigel: *Metal Ions in Biological Systems*, Vol. 7. Dekker, New York 1978, cf. [17].
[3] Cf. R. E. Dickerson, *Sci. Am. 239* (1978) issue 3, 62.
[8] A. Müller, U. Reinsch, *Angew. Chem. 92* (1980) 69; *Angew. Chem. Int. Ed. Engl. 19* (1980) 72.
[14] P. C. H. Mitchell, C. F. Pygall, *J. Inorg. Biochem. 11* (1979) 25.
[17] Cf. A. Müller, E. Diemann, R. Jostes, H. Bögge, *Angew. Chem. 93* (1981) 957; *Angew. Chem. Int. Ed. Engl. 20* (1981) 934; A. Müller, W. Eltzner, H. Bögge, unpublished.

Fixation of the Dithiosulfate Ion $S_3O_2^{2-}$; Preparation, Crystal Structure, and ESCA Spectrum of $(PPh_4)_2[(S_2)OMoS_2MoO(S_3O_2)]$

By *Achim Müller**, *Uta Reinsch-Vogell*, *Erich Krickemeyer*, and *Hartmut Bögge*

Previous attempts to isolate $S_3O_2^{2-}$ as the salt, or to stabilize it by complexation, have not met with success. We have now been able to fix by complexation the $S_3O_2^{2-}$ formed on oxidation of S_x^{2-} ligands in a metal complex with oxygen. Such reactions are relevant to the metabolism of phototrophic microorganisms which oxidize S^0 or S^{2-} and are effective in the sulfur cycle[1]. The reaction is, however, also of interest for an understanding of the oxidation of simple "sulfur species".

When a solution of $(PPh_4)_2MoOS_3$ and sulfur in acetonitrile [Reaction (a)] or of $(PPh_4)_2MoS_4$ in dimethylformamide [Reaction (b)] is exposed to oxygen, gradual formation of brown, crystalline $(PPh_4)_2[(S_2)OMoS_2MoO(S_3O_2)]$ **1** is observed. As shown by an X-ray structure analysis [Cc, $a = 2082.4(9)$, $b = 1364.6(8)$, $c = 1885.7(8)$ pm, $\beta = 108.98(3)°$, $V = 5066.9 \times 10^6$ pm^3, $Z = 4$; $R = 0.062$ for 4124 reflections] an S_2^{2-} as well as the bidentate dithiosulfate ligand $S_3O_2^{2-}$ are coordinated to the known central $OMoS_2MoO$ unit[2] in the complex anion of **1** (cf. Fig. 1 with atomic distances). As expected, the average SS distance in the dithiosulfate ligand is longer, the average SO distance somewhat shorter than in the "isolated" $S_2O_3^{2-}$ **2** (*ca.* 200 and 146 pm[1b], respectively). The OSS angles [110.5(7), 110.2(6), 110.6(6), 112.1(6)°] have values about the same as in the regular tetrahedron or as in **2**, whereas the SSS angle [96.2(2)°] is expectedly smaller and the OSO angle [115.6(9)°] correspondingly larger than the OSS bond angles. Asymmetrically coordinated complexes containing the $OMoS_2MoO$ moiety are already known.

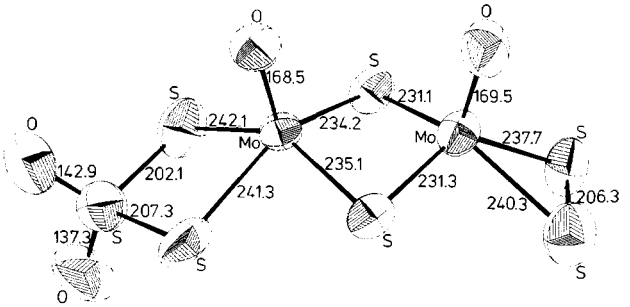

Fig. 1. Structure of the complex anion in crystals of **1**. Maximum standard deviations (in pm): Mo—S 0.5; S—S 0.7; Mo—O 1.1; S—O 1.5.

The $S_3O_2^{2-}$ ligand can be visualized nicely by the ESCA method: besides an S-2p signal at 162.7 eV (for a total of six "sulfidic" sulfur atoms in **1**, *i.e.* two from the dithiosulfate and four others) a signal is observed at 168.6 eV (for S^{+VI}) in the intensity ratio 6 : 1; E_B(Mo-3d$_{5/2}$) appears at 230.3 eV (all values relative to E_B(C-1s$_{1/2}$) = 285.0 eV). The ligand also shows characteristic IR bands in the solid state spectrum (KBr pellet) of **1**: $\nu_{as}(SO_2) = 1255$, $\nu_{as}(SS_2)/\delta(SO_2) = 598$, 557 cm^{-1}; ν(MoO) = 955 cm^{-1}.

Very little is known about the oxidation of S_x^{2-} ligands ($x = 1-5$). In the present case, $S_3O_2^{2-}$ *could* be schematically formed in reaction (a) (without considering redox processes[2a]; *i.e.* reduction of Mo^{VI}) according to

$$\{Mo(S^{2-})\} \xrightarrow{S_x} \{Mo(S_4^{2-})\} \xrightarrow[-S]{} \{Mo(S_3^{2-})\} \xrightarrow{O_2} \{Mo(S_3O_2^{2-})\}$$

(by activation of S_3^{2-} and stabilization of $S_3O_2^{2-}$ on Mo), since the complex $[(S_4)OMoS_2MoO(S_4)]^{2-}$ is formed (together with $[OMo(S_4)_2]^{2-}$) in the same reaction—but under N_2[2a]. In reaction (b), MoS_4^{2-} could furnish the fragment $\{Mo(S_3^{2-})\}$, which should react further according to (a)[3].

In the sulfur cycle, which is important for the biosphere and our ecosystem, microorganisms are effective which reduce SO_4^{2-} (by assimilatory reduction but also in "sulfate respiration"), or which oxidize reduced species such as S^{2-} or S^0, like the phototrophic prokaryotes Chromatiaceae and Chlorobiaceae. Possibly, not only sulfur-rich anions such as $S_2O_3^{2-}$ [1] are formed in the photosynthetic processes, but also previously undetected species such as $S_3O_2^{2-}$ (*e.g.* as intermediates).

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CAS Registry numbers:
1, 83061-14-7; $(PPh_4)_2MoOS_3$, 83061-15-8; S, 7704-34-9; $(PPh_4)_2MoS_4$, 14348-10-8

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[1] a) H. Bothe, A. Trebst: *Biology of Inorganic Nitrogen and Sulfur*, Springer-Verlag, Berlin 1981; b) B. Meyer: *Sulfur, Energy and Environment*, Elsevier, Amsterdam 1977.

[2] Cf. a) A. Müller, E. Diemann, R. Jostes, H. Bögge, *Angew. Chem. 93* (1981) 957; *Angew. Chem. Int. Ed. Engl. 20* (1981) 934; b) W. Clegg, N. Mohan, A. Müller, A. Neumann, W. Rittner, G. M. Sheldrick, *Inorg. Chem. 19* (1980) 2066; A. Müller, W. Jaegermann, *Coord. Chem. Rev.*, in press.

[3] *Procedure:* $(PPh_4)_2MoS_4$ (0.6 g) was added to dimethylformamide (p.a.; 25 mL) in a 100 mL Erlenmeyer flask. The mixture was stirred at 20 °C under N_2 until dissolution was complete. After addition of 25 mL of anhydrous ethanol (p.a.) the mixture was heated at 60 °C for 15 min, whereupon reprecipitated $(PPh_4)_2MoS_4$ was essentially dissolved. The flask was stoppered and allowed to stand at 20 °C for 16 h (all operations were carried out under N_2). The solution was filtered in presence of air, and the filtrate stored in a closed vessel at 20 °C for 14 d. The reaction mixture was then treated with 75 mL of ethanol and once again allowed to stand for 16 h at 20 °C in a stoppered 250 mL Erlenmeyer flask. The precipitated reddish-brown crystals were filtered off, washed with anhydrous EtOH, CS_2, and Et_2O and dried in a vacuum (yield 0.15 g). **1** cannot be obtained in the pure state using reaction (a).—In a modified method (b), either the novel black "mixed valence" complex $(PPh_4)_2[(S_2)OMo^{V}S_2Mo^{V}O(Mo^{VI}S_4)]$ (characterized by crystal structure determination), or the monothiosulfate complex corresponding to **1** can be obtained.

BOOK REVIEWS

Kinetics and Mechanism. A Study of Homogeneous Chemical Reactions. By *J. W. Moore* and *R. G. Pearson*. 3rd edition, Wiley-Interscience, Chichester 1981. xv, 455 pp., bound, £ 23.70.

For the generation of chemists who first came into contact with chemical kinetics in the 'fifties and 'sixties "Frost-Pearson" was a standard introductory textbook and review of the field of homogeneous reaction kinetics[*]. A new edition of "Kinetics and Mechanism" by *J. W. Moore* and *R. G. Pearson* has now appeared after 20 years, and the expectations are naturally running high, in view both of the renown of the older work and the competition that has meanwhile arisen from other monographs in this field. It is a pleasure to say that these expectations can be regarded as having been satisfied. Through a far-reaching revision of the book (about four-fifths of it has been newly written) it has been possible to include the developments of the last 20 years so successfully that the new work constitutes an excellent review of the present state of kinetics and of its concepts, methods, and applications in the clarification of reaction pathways.

The classification of the material has remained substantially unchanged from the second edition. The number of detailed examples of elucidated reaction mechanisms has been drastically cut down to make room for the treatment of more recent theoretical and experimental developments, and the previous two concluding chapters have been eliminated. The book opens with a discussion of the empirical foundations for the treatment of rate constants, and goes on with a chapter on experimental methods and the analysis of kinetic measurements in which—as in a later chapter on complex systems—the appropriate use of computers in data analysis, numerical integration, and simulation with models is also briefly considered. The chapters "Collisions between Molecules" and "Potential Surfaces and the Theory of the Transition State" treat current theoretical concepts and principles for the analysis and calculation of homogeneous reactions under the common term of "elementary processes". Some important and topical aspects such as the pressure dependence of unimolecular processes or problems on energy transfer between and within molecules are discussed in the following chapter which, however, is mainly devoted to experimental examples from the standpoint of interaction between theory and experiment. This is followed by the treatment of neutral and ionic reactions in solutions. Formal and experimental aspects of composite reaction pathways are the subject of the next chapter, on "Complex Reactions". A longer chapter deals with homogeneous catalysis, and finally with chain reactions and—only very briefly—with photochemistry.

The text is unfailingly very clear and comprehensible and, with about 800 references (up to 1980!), it is prepared carefully with an eye to further study. The idea of communicating basic principles and central results so plainly that the reader acquires a sound basis for direct independent applications is everywhere in evidence. Thus, there are sound discussions on the prerequisites (*e.g.* the theory of the transition state or the concept of the steady state) and a detailed notation of equations and their derivations are given. All this is most helpful to the user. The high degree of balance between theoretical explanations and application-oriented preparation makes the book particularly suitable for the experimental scientist, even if only a potential one. Of course, one could always criticize this or that detail, but such objections pale into insignificance in comparison with the sheer solid worth of the book.

Summarizing, this new edition of "Kinetics and Mechanism" can be recommended without any reservations to the advanced student and to the practising scientist who from inclination or necessity wants a new general account and concrete access to kinetics. Those already experienced in kinetics will find it useful as a handy and rapidly accessible work of reference.

Klaus Luther [NB 567 IE]

Structure and Bonding in Crystals. Volume 1. Edited by *M. O'Keefe* and *A. Navrotsky*. Academic Press, New York 1981. xviii, 327 pp., bound, $ 48.00.

This is the first of two volumes containing the material of a conference on solid-state problems. It comprises 13 chapters—writen by 17 authors—each giving a unified account of one aspect of the solid state. The book must be praised for its sturdy appearance and many references, the latter enabling the interested reader to learn more about the background and the problems associated with the 13

[*] Cf. *Angew. Chem. 73* (1961) 719.

topics, whose treatment is far from being uniformly comprehensive. Five chapters are devoted to approaches to the description of the structure and bonding in solids on the basis of the pseudopotential theory, and of these *A. Zunger*'s particularly exhaustive and comprehensible contribution stands out from the point of view of the practical chemist. *Zunger* demonstrates using numerous examples the significance and usefulness of orbital radii, *e.g.* for classifying a large number of crystal structures, and shows how the orbital radii are connected with some classical concepts such as electronegativities and atomic radii. On the other hand, the description of the formalism for the elementary quantitative theory of the chemical bond is somewhat abstract and very difficult to follow, owing to the lack of detailed examples (this theory can be used for practical applications with the aid of a pocket calculator). *W. A. Harrison*'s own book on this topic must be considered the most important reference in this connection. The other chapters deal with ways of applying some semiquantitative methods of the MO theory to the question of bonding in solids, these methods being derived from molecular chemistry, where they have been used with great success. Such approaches will certainly gain importance in the future, even though the purists among the theoreticians do not entirely take them seriously. Reminiscences of the classical ionic model of chemical bonding in solids and a historical survey by *L. Pauling*, extremely enjoyable as vacation reading, complete the book, which on the whole creates a favorable impression. Despite the suggestion in the preface, however, the book cannot compete with *Pauling*'s own "Nature of the Chemical Bond" and will not become its successor in the literature. This is not so much because of its contents as because it necessarily lacks the didactically unified form of *Pauling*'s textbook, being a collection of 13 separate contributions (with another 13 to come in the second volume).

Hans-Jörg Deiseroth [NB 570 IE]

Bioorganic Chemistry. By *H. Dugas* and *C. Penney*. Springer-Verlag, Berlin 1981. xii, 508 pp., bound, DM 59.00.

It is probably true to say that few chemists know precisely the meaning of "bioorganic chemistry", and it was therefore wise to provide the subtitle (A Chemical Approach to Enzyme Action) and to give immediately (in the Preface) a definition of this recent discipline:

"Bioorganic chemistry" is the application of the principles, models, and methods of organic chemistry to the understanding of biological processes.

The field is sketched broadly with skilfully selected examples in an introductory chapter. Studies of enzymatic processes on natural systems are described side by side with investigations on simple synthetic models which make it possible to study effects without the disturbing influence of accompanying parameters. Knowledge of the complex-forming properties of molecules, on the one hand, and of enzymes and enzyme models on the other hand, should lead to structure-activity relationships invaluable for the directed synthesis of biologically active compounds such as pharmacological agents. Knowledge obtained on enzymes and models concerning reactivity, with the involvement of electronic, steric, and stereoelectronic effects and neighboring group effects, should make it possible to design tailor-made molecules whose catalytic activity at least approaches that of biological systems.

Not only the contents but also the similar classification of the next two chapters demonstrate the close correlation between the basic building blocks of life, nucleic acids and proteins.

The structure and chemical reactivity of the monomeric nucleotide and amino-acid units are compared with one another and brought into relationship with problems of the synthesis and biosynthesis of oligomers. What I believe to be particularly useful for students, at whom this book is also directed, is that analogies from "ordinary" organic chemistry are brought in again and again for the sake of clarification. The chapter on nucleic acids ends with an excellent digression on the chemical evolution of organic molecules, in which light is also thrown on the problem of the origin of chiral molecules.

Using all the tools of organic chemistry, *e.g.* conformational analysis and stereoelectronic control of reactions, the authors then acquaint the reader by means of selected examples with the problems of enzyme catalysis and prepare him for the chapter on enzyme models.

On the examples of chiral crown ethers, polymers, and micelles it is demonstrated here in what manifold ways these "artificial enzymes" perform selective complexing reactions, stereoselective transport, and catalytic functions. Also inspired by nature are biomimetic reactions, which are explained using phenol oxidations and terpene cyclizations.

The next chapter deals with the role of metal ions in enzyme reactions. The choice of the very well researched iron-containing hemoglobin and of vitamin B_{12}, and also of suitable synthetic models is very appropriate from the didactic point of view. Regrettably, there is no mention of photosynthesis as an important primary biochemical process.

The concept of comparing natural systems with artificial models is followed consistently in the last chapter on coenzymes with emphasis on chemoselectivity and stereoselectivity.

Summarizing, it may be said that whereas for students the book offers a good introduction into the field, the advanced reader will also find a wealth of suggestions and see many problems in new perspectives. A literature index which contains mainly review articles is useful for identifying the original literature. The book can also be recommended because of its relatively low price.

Franz Peter Montforts [NB 569 IE]

Polarographische Analyse. By *M. Geissler*. Verlag Chemie, Weinheim 1981. 194 pp., bound, DM 73.00.

This monograph is divided into seven chapters. After a brief historical introduction it covers as much of the theory of electrochemical kinetics as is needed by the practical analytical chemist. The principles of the various voltametric methods are discussed on the basis of the 1976 IUPAC recommendations for electrochemical analysis. From the point of view of practical trace analysis, the author does not put enough stress on the methods essential for this type of analysis. For example, inverse voltammetry, which is particularly important for trace analysis, should have been described in much greater detail, while a mere mention would have sufficed in the case of oscillopolarography, which is hardly ever used nowadays. The next chapter, on the theory of methods involving different types of polarization, will be a useful source of practical information.

However, when it comes to discussing the technical aspects, the analytical side again comes off inadequately. Thus, in the case of electrodes, the mercury film electrodes important for ultratrace analysis receive only sketchy treatment. There are also large gaps in the description of modern commercial polarographs and their analytical performance. In this respect the book lags behind practical developments, and indeed in some cases far behind them.

However, it is mainly in the last two chapters, dealing with analytical applications, that the book does not live up to the expectations suggested by its title in chemists engaged in trace analysis. It does not give a full account of the various possibilities and the many fields of application in the reliable and highly sensitive trace analysis of metals and organic substances. At best, it only gives impressions of these. From this point of view, the monograph does not do full justice to its title.

The forte of the work lies undoubtedly in its succinct and didactically successful treatment of the principles of polarographic methods and the theory of electrode processes. In this respect this highly readable book will be useful to analytical chemists not very familiar with electrochemistry and polarography.

Hans W. Nürnberg [NB 571 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 (Federal Republic of Germany).

Structure and Bonding. Vol. 51: Electron Nuclear Double Resonance of Transition Metal Complexes with Organic Ligands. By *A. Schweiger*. Springer-Verlag, Berlin 1982. vii, 128 pp., bound, DM 74.00.—ISBN 3-540-11072-0

Topics in Current Chemistry. Vol. 101: Host-Guest Complex Chemistry II. Edited by *F. Vögtle*. Springer-Verlag, Berlin 1982. viii, 203 pp., bound, DM 88.00.—ISBN 3-540-11103-4

Physics and Chemistry of the Shroud of Turin. Summary of the 1978 Investigation by *L. A. Schwalbe* and *R. N. Rogers*. Elsevier Scientific Publishing Company, Amsterdam 1982, 49 pp.

Inorganic Chemistry Concepts. Vol. 6: Inorganic Stereochemistry. By *D. L. Kepert*. Springer-Verlag, Berlin 1982. xii, 227 pp., bound, DM 154.00.—ISBN 3-540-10716-9

Lecture Notes in Chemistry. Vol. 28: Symmetry Properties of Molecules. By *G. S. Ezra*. Springer-Verlag, Berlin 1982. viii, 202 pp., bound, DM 39.80.—ISBN 3-540-11184-0

The Handbook of Environmental Chemistry. Vol. 2, Part B. Anthropogenic Compounds. Edited by *O. Hutzinger*. Springer-Verlag, Berlin 1982. xvii, 210 pp., bound, DM 116.00.—ISBN 3-540-11108-5

Chronicles of Drug Discovery. Vol. 1. Edited by *J. S. Bindra* and *D. Ledniger*. John Wiley & Sons, New York 1982. dxvi, 283 pp., bound, £ 24.00.—ISBN 0-471-06516-1

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Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins. Vol. 6. Edited by *B. Weinstein*. Marcel Dekker, Basel 1982. x, 327 pp., bound, Sfr. 148.00.—ISBN 0-8247-1363-X

Catalysis. Science and Technology. Vol. 2. Edited by *J. R. Anderson* and *M. Boudart*. Springer-Verlag, Berlin 1981. x, 282 pp., bound, DM 132.00.—ISBN 3-540-10593-X

Herstellung selektiver chelatbildender Ionenaustauscher zur Anreicherung von Metallen. Forschungsberichte des Landes Nordrhein-Westfalen. Heft 3070/Fachgruppe Physik/Chemie/Biologie. Issued by Minister für Wissenschaft und Forschung. Westdeutscher Verlag, Opladen 1981. II, 22 pp., bound, DM 8.00.—ISBN 3-531-03070-1

Der Schutz wissenschaftlicher Forschungsergebnisse. By *F.-K. Beier* and *J. Straus*. Verlag Chemie, Weinheim 1982. viii, 116 pp., bound, DM 48.00.—ISBN 3-527-25940-6

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Hobby- und Haus-Chemie. Rezepturen - neu zusammengestellt. By *B. Ziolkowsky*. Verlag für Chemische Industrie H. Ziolkowsky KG, Augsburg 1982. 204 pp., bound, DM 45.00.—ISBN 3-87846-107-0

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The Role of Frontier Orbitals in Chemical Reactions (Nobel Lecture)**

By Kenichi Fukui*

Introduction

For more than a thousand years chemistry has been thought of as a complicated, hard-to-predict science. Efforts to improve even a part of its unpredictable character first bore fruit through the success of the "electronic theory". This was founded mainly by organic chemists, such as *Fry, Stieglitz, Lucas, Lapworth,* and *Sidgwick,* brought to a completed form by *Robinson* and *Ingold,* and later developed by many other chemists[1]. In the electronic theory, the mode of migration of electrons in molecules is considered under various aspects. For this purpose a criterion is necessary for the number of electrons which should be assigned to an atom or to a bond in a molecule. Therefore, it can be said that the concept of the sharing of electrons, proposed by *Lewis,* gave a firm basis to the electronic theory[2].

In the theory of organic chemistry the terms acid/base, oxidation/reduction, and so on have been profitably utilized for some time. Furthermore, there are terms centering more closely around the electron concept, such as electrophilicity/nucleophilicity and donor/acceptor.

It should be mentioned that these pairs of terms can be qualitatively related to the scale of electron density or electric charge. In the electronic theory, the static and dynamic behavior of molecules are explained by the electronic effects which are based solely on the distribution of electrons in a molecule.

The charge distribution in a molecule can be sketched to a certain extent using the electronegativity concept of atoms, in conjunction with chemical experience. It is given foundation, made quantitative, and supported by physical measurements and theoretical calculations based on quantum theory.

The distribution of electrons or electric charge—the result is the same irrespective of which is used—in a molecule is usually represented by the total number (generally non-integer) of electrons in each atom and each bond. This concept was easily acceptable, even to experimental chemists, as having a tolerably realistic meaning. Therefore, chemists used electron density as a fundamental concept for the explanation of various phenomena. In particular, in devising novel chemical reactions researchers usually rely upon analogy through experience, and here electron density was very effectively and widely used as the basic concept.

When the magnitude of the electron density is adopted as the criterion, the electrostatic attraction and repulsion caused by the electron distribution are taken into account. Therefore, it is reasonable to infer that an electrophilic reagent will attack the center of high electron density in a molecule, whereas a nucleophilic reaction will occur at the center of low electron density. In fact, *Wheland* and *Pauling*[3] explained the orientation of substitutions in benzene and its compounds along these lines, and analogous interpretations of the mode of many other chemical reactions followed in the same fashion.

However, the question as to why one of the long-known, simple reactions, such as the electrophilic substitution of naphthalene, *e.g.* by nitration, predominantly yields 1-substituted derivatives was not so easy to answer. This is because in many unsubstituted aromatic hydrocarbons both the electrophile and the nucleophile react at the same center. This point cast some doubt on the theory of organic reactivity, where exclusively the electron density was thought to be decisive.

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The Concept of Frontier Orbital Interactions

The solution of this reactivity problem was attempted by many people from numerous angles. Above all, *Coulson* and *Longuet-Higgins*[4] investigated the change of electron density distribution under the influence of the approaching reagent. The explanation proposed by *Wheland*[5] was based on the calculation of the energy required to localize electrons at the site of reaction. But I myself tried to attack this problem in a way which was at that time slightly unusual. Bearing in mind the principal role played by the valence electrons in the formation of molecules from atoms, only the distribution of the electrons occupying the highest energy π orbital of aromatic hydrocarbons was calculated. The results were more successful than expected, and an almost perfect agreement between the actual position of electrophilic attack and the site of highest electron density calculated for the highest occupied π orbital was found, as shown in Figure 1[6].

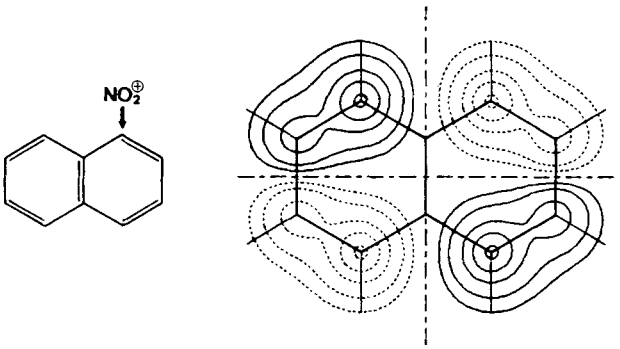


Fig. 1. Nitration of naphthalene.

The "orbital" concept, which was established and developed by many scientists—*Pauling, Slater, Mulliken, Roothaan, Löwdin, Hückel, Parr* and so on—had till then been used to construct wave functions of molecules by means of which molecular properties were usually interpreted[7]. It also seemed that the electron distribution in an orbital was directly connected to chemical observations, and this fact was certainly felt to be interesting by many chemists.

But the result of such an "extravagant" attempt was by no means readily accepted by the majority of chemists. The publication[6] received a number of controversial comments. This was in a sense understandable, because due to my lack of experience the theoretical foundation for our notable result was obscure or rather improperly presented. However, it was fortunate for me that the work of *Mulliken*[8] on charge-transfer complexes was published in the same year.

The model of *Mulliken et al.* for protonated benzene was very helpful[9]. Our work in collaboration with *Yonezawa, Nagata,* and *Kato* provided a simple and clear picture of the theoretical interpretation of reactions[10]. In a similar way the "overlap and orientation" principle proposed by *Mulliken* enabled the orientation in molecular complexes[11] to be clarified. Subsequent to electrophilic substitution, nucleophilic substitution was discussed and it was found that here the lowest unoccupied orbital was decisive[12]. In reactions with radicals, both of the two orbitals mentioned previously become the "essential" orbitals.

There was no reason to limit these essential orbitals to π orbitals, so that the method was applied not only to unsaturated but also to saturated compounds. The fact that it could be applied to saturated compounds was a substantial advantage compared to many theories of reactivity which were limited only to π electron compounds. The method displayed its particular usefulness in studying the abstraction of hydrogen from aliphatic hydrocarbons by radicals, the S_N2 and E2 reactions of halogenated hydrocarbons, the nucleophilic abstraction of α-hydrogen atoms from alkenes, and so forth[13].

The two molecular orbitals which play an essential role in a wide range of chemical reactions of saturated or unsaturated compounds were referred to under the general term "frontier orbitals", abbreviated frequently by HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital).

The validity of the theory gradually became clearer. The vein of ore discovered by chance was found to be more extensive than expected. But it was the role played by the symmetry of the "essential" orbital, pointed out in 1964 with regard to Diels-Alder reactions[14], that broadened the utility of our studies further. It was found, as seen in Figure 2, that the symmetries of the HOMO and LUMO of dienes and of the LUMO and HOMO of dienophiles, respectively, are in an extremely favorable situation for a concerted cyclic interaction.

This led to two important aspects: Firstly, it pointed out a possible correlation between the orbital symmetry and the rule determining the occurrence or non-occurrence of a chemical reaction, which may be called the "selection rule", in common with the selection rule in molecular spectroscopy. Secondly, it provided a clue to discuss what was the "concertedness" in a reaction which proceeds *via* a cyclic conjugation of electrons.

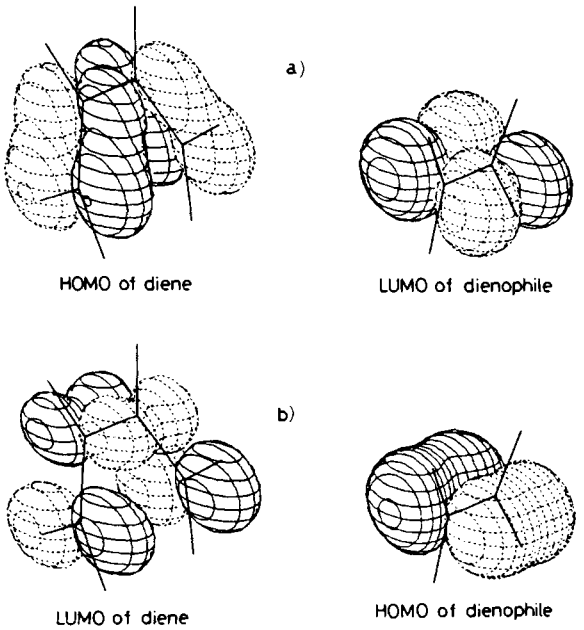


Fig. 2. The significance of orbital symmetry in the HOMO-LUMO overlap in Diels-Alder reactions.

In 1965 *Woodward* and *Hoffmann* proposed the stereoselection rules which are known today as the "Woodward-Hoffmann" rules[15,16]. An experimental result developed by *Havinga et al.*[17] was, herewith, extended immensely. It was only after the appearance of the brilliant work by *Woodward* and *Hoffmann* that I became fully aware that not only the electron density distribution but also the nodal properties of the essential orbitals have significance in a wide variety of chemical reactions. In fact, we previously studied the classical (4n+2) rule proposed by *Hückel*[8], and noticed that the sign of the bond order in the highest occupied orbital of an open-chain conjugation system should be closely related to the stabilization of the corresponding conjugated rings[19]. We did not imagine, however, that the discussion might be extended to the so-called Möbius-type ring-closure![20]

By considering the HOMO-LUMO interactions between the fragments of a conjugated chain divided into two parts[21], frontier orbital theory can yield selection rules which are absolutely equivalent to those obtained from the "conservation of orbital symmetry" principle of *Woodward* and *Hoffmann*. One point I may stress here is, as suggested by *Fujimoto, Inagaki,* and I[22], that the electron delocalization between the "essential" orbitals exactly expresses, in terms of orbital symmetries, the formation and breaking of chemical bonds which, I believe, should be of key importance for perceiving chemical processes.

In the cycloaddition of butadiene and ethylene shown in Figure 2, both the interaction between the HOMO of the diene and the LUMO of the dienophile, and that between the LUMO of the diene and the HOMO of the dienophile stabilize the reacting system. If one is interested in the spatial properties of interaction, however, one may recognize the clear distinction between the roles of the two types of orbital interactions. The HOMO of ethylene and the LUMO of butadiene are both symmetric with respect to the symmetry plane retained throughout the course of cycloaddition. This signifies that each of the carbon atoms of ethylene is bound to both of the terminal carbons of butadiene. The chemical bonding between the diene and dienophile thus generated may resemble that in a loosely bound complex, *e.g.*, protonation of an olefinic double bond. In contrast, the HOMO of butadiene and the LUMO of ethylene are antisymmetric. The interaction between these orbitals leads, therefore, to two separated chemical bonds, each of which links a carbon atom of ethylene and a terminal carbon atom of butadiene. Needless to say it is the interaction between the HOMO of the diene and the LUMO of the dienophile that is decisive for the occurrence of a concerted cycloaddition[22].

In the course of time it was discovered that the electron delocalization between the HOMO and LUMO is generally the principal factor determining the ease of a chemical reaction and its stereoselective path, irrespective of whether an intra- and intermolecular processes occurs (Fig. 3). Besides our work, a number of other research groups have made contributions to this area.

First of all, the general perturbation theory of HOMO-LUMO interaction between two molecules was built up by *Salem et al.*[23-25]. One of *Salem*'s papers[25] was in line with the theory of *Bader*[26], which specified the mode of

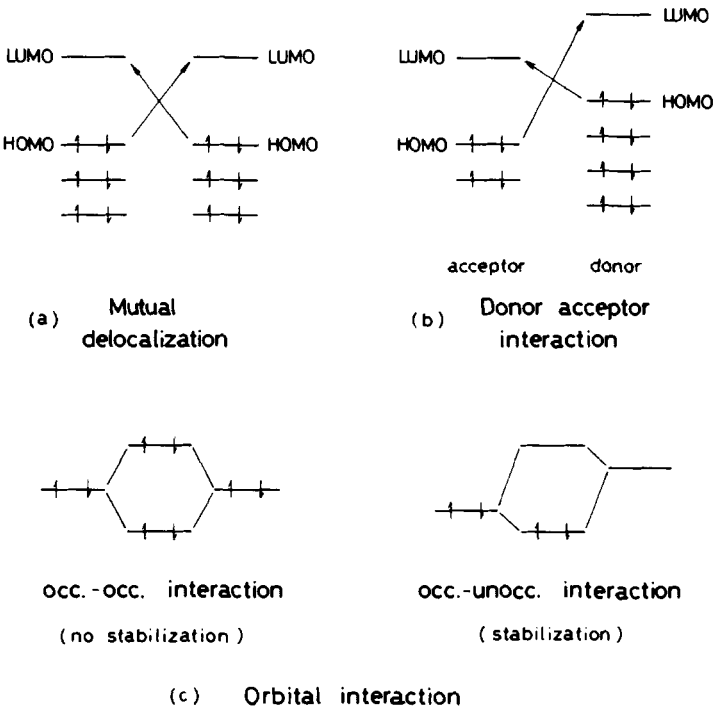


Fig. 3. The mode of interaction between orbitals of two molecules.

decomposition of a molecule or of a transition complex by means of the symmetry of the normal vibration. Furthermore, *Pearson*[27] investigated the relationship between the symmetry of reaction coordinates and that of the HOMO and LUMO.

The discussion so far may seem to overestimate the importance of these selected orbitals, HOMO and LUMO. This point was ingeniously modified by *Klopman*[28]. He carefully took account of the factors to be considered in the perturbation theory of reacting systems, and classified reactions into two types

- the first was the "frontier-controlled" case, in which the reaction was controlled by the "essential" orbital interaction, and
- the second was the "charge-controlled" case, where it was controlled by the electrostatic interaction of charges.

This classification was widely and successfully used. In this context, the review articles of *Herndon*[29] and of *Hudon*[30] proved to be very useful. The names of *Coulson*[4] and *Dewar*[31] should also be mentioned here as having made contributions to the development of theories of reactivity.

Returning to the subject again, let us imagine that two molecules approach each other and that orbital overlap takes place. Application of perturbation theory[32] to this sort of interaction indicates that the larger the orbital overlap and the smaller the energy level separation of the two overlapping orbitals, the larger is the contribution of the orbital pair to the stabilization of an interacting system. Accordingly, at least initially, a reaction will proceed with

a mutual nuclear configuration which is most favorable for the HOMO-LUMO overlap.

Now let us suppose that a flow of electrons occurs from the HOMO of molecule I to the LUMO of molecule II. In each molecule the bonds between the reaction center—the site at which the orbitals overlap with those of the other molecule—and the remaining part of the molecule are weakened. In this case, the bonding relationships in the HOMO of molecule I are weakened and the antibonding strengthened, while in molecule II the antibonding relationships in the LUMO are weakened and those bonding strengthened. Consequently, the HOMO of molecule I is particularly destabilized relative to the other occupied orbitals, and among the unoccupied orbitals the LUMO of molecule II is selectively stabilized, so that the HOMO-LUMO level separation between the two molecules is decreased. Such a set of circumstances is clearly seen in Figure 3.

When such bond weakenings have arisen the HOMO and the LUMO tend to become more localized at these weakened bonds in each molecule. In addition, the weakening of the bonds between the reaction center and the remaining part of the molecule causes an increase in the amplitudes of the HOMO and the LUMO at the reaction centers, resulting in a larger overlap of the HOMO and the LUMO[33]. Such a trend of the characteristic change in the orbital pattern is confirmed by numerical calculations. The role of the interaction between the HOMO and the LUMO turns out to become more and more important as the reaction proceeds.

A series of studies on chemical interactions was attempted in which the interaction of reactants was divided into the Coulombic, the exchange, the polarization, and the delocalization interactions, and their respective contributions to the interaction energy were quantitatively discussed[32, 34]. In this way the dimerization[35] and the addition of methylene to ethylene[36], the dimerization of BH_3[37], and also several donor-acceptor interactions, *e.g.* BH_3-NH_3[38], BH_3-CO[39], NH_3-HF[40], *etc.*, were discussed. The method was also applied to reactions of radicals, such as the abstraction of a hydrogen atom from methane by a methyl radical, the addition of a methyl radical to ethylene[41], and recombinations, disproportionations, and self-reaction of two radicals[42]. In these calculations, the configurational analysis proposed originally by *Baba et al.*[43] was also found to be useful. We were able to show numerically the increase in electron delocalization from the HOMO to the LUMO as the reaction proceeded, the increasing importance of the contribution of such a delocalization to the stabilization of the reaction system, and the driving force of the reaction in terms of orbital interactions, among others.

The question: "Why do the HOMO and the LUMO solely determine the reaction path?" was one which I was frequently posed by audiences at my lectures. The discussion so far should correspond, at least in part, to that answer. But one may not overestimate the importance of the HOMO and the LUMO. In one-center reactions, such as substitutions, in which the orbital symmetry plays no role, any occupied orbitals which are very close in energy to the HOMO should properly be taken into account[12]. In large alkane molecules a number of HOMO's (high-lying occupied MO's) and furthermore, as will be referred to later, in metal crystals even the "HOMO-band" must be taken into account. If the HOMO or the LUMO happens to be inadequate owing to its extension, symmetry, or nodal properties, the next orbital should be sought. One of the simplest examples of such an instance is the protonation of pyridine. In this case, the nitrogen lone-pair orbital is not the HOMO, but the addition of a proton to the nitrogen lone-pair so as not to disturb the π conjugation, will evidently be more advantageous than addition to higher occupied π orbitals, which may interrupt this. The reason why the proton dare not add to the positions of high amplitude of the π HOMO in this case is thus understood. It is not satisfactory to treat a disagreement between the HOMO-LUMO argument and an experimental result formally as an *exception* to the theory. A so-called exception has its own causes, and the investigation of these causes may possibly yield a novel result.

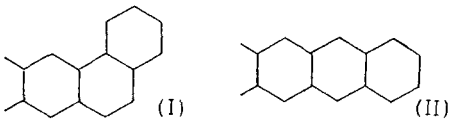
The HOMO-LUMO interaction argument was recently pointed out[44] to be useful, in an auxiliary sense, for interpreting the sign of a reaction constant and the substituent constant scale in the Hammett rule[45], which has made an immeasurable contribution to the study of substituent effects upon chemical reactivity. In cyclic additions, such as Diels-Alder reactions and 1,3-dipolar additions, the relative ease of occurrence of reactions, various subsidiary effects and interesting phenomena, such as regioselectivity and periselectivity, were interpreted with considerable success simply by knowing the height of the energy level of the HOMO and the LUMO, the mode of their extension, and their nodal structure, *etc.*[46]—I defined these as the *orbital pattern*.

Other topics that have been discussed in terms of HOMO-LUMO interactions are thermal formation of excited states[47], singlet-triplet selectivity[48], the chemical property of diradicals and excited states[49], the interaction of the central atom and ligands in transition-metal complexes[50], the interaction of three or more orbitals[51], and so forth. *Inagaki et al.* extended the theory to include the polarization effect on the HOMO and the LUMO due to mixing with other orbitals, and gave an elucidation of a number of problems in organic chemistry which were not always easy to explain: the unique stereoselectivity in transannular bond formation, the lone-pair effect, the d orbital effect, and the orbital polarization effect due to substituents[52].

As previously discussed, the method of orbital interaction was applied not only to the ground electronic state but also to excited states, giving rise to an explanation of the path of even complicated photochemical isomerizations[13, 21]. In the majority of cases the HOMO and the LUMO of the ground-state molecule were also found to be the essential orbitals. Even the ground-state reaction of a strong electron acceptor (or donor) causes a mixing with an ionized electron configuration or an excited electron configuration in another molecule. In consequence, a partial HOMO-HOMO or LUMO-LUMO interaction, which would be trivial without the influence of the acceptor (or donor), becomes important in stabilizing the interacting system[47].

The problems so far discussed have been limited to chemical reactions. However, the HOMO-LUMO interaction must also come into bearing in other chemical phenomena in almost the same way—with the exception that they usually do not bring about such a remarkable change in the nuclear configuration. Now let us examine the possibility of applying the theory to "aromaticity"—one of the simplest, but hardest-to-interpret problems. There seem to be few problems so frustrating to theoreticians as the explanation of this classical chemical concept. I greatly appreciate the contribution of *Dewar*'s theory[53, 54] based on quantitative energy calculations. Here, however, I want to give a qualitative comment from an entirely different point of view.

It is easily ascertained[55] from Figure 4 that in benzene, naphthalene, and phenanthrene, *etc.*, any conceivable division of the molecule into two fragments always produces segments whose HOMO and LUMO overlap in-phase at the original two junctions. But these circumstances are not observed in anthracene, which is usually viewed as one of the typical examples of an aromatic compound. *Hosoya*[55] pointed out from comparison with phenanthrene (see Fig. 4) that annelation of type (II) is less stable than that of type (I).



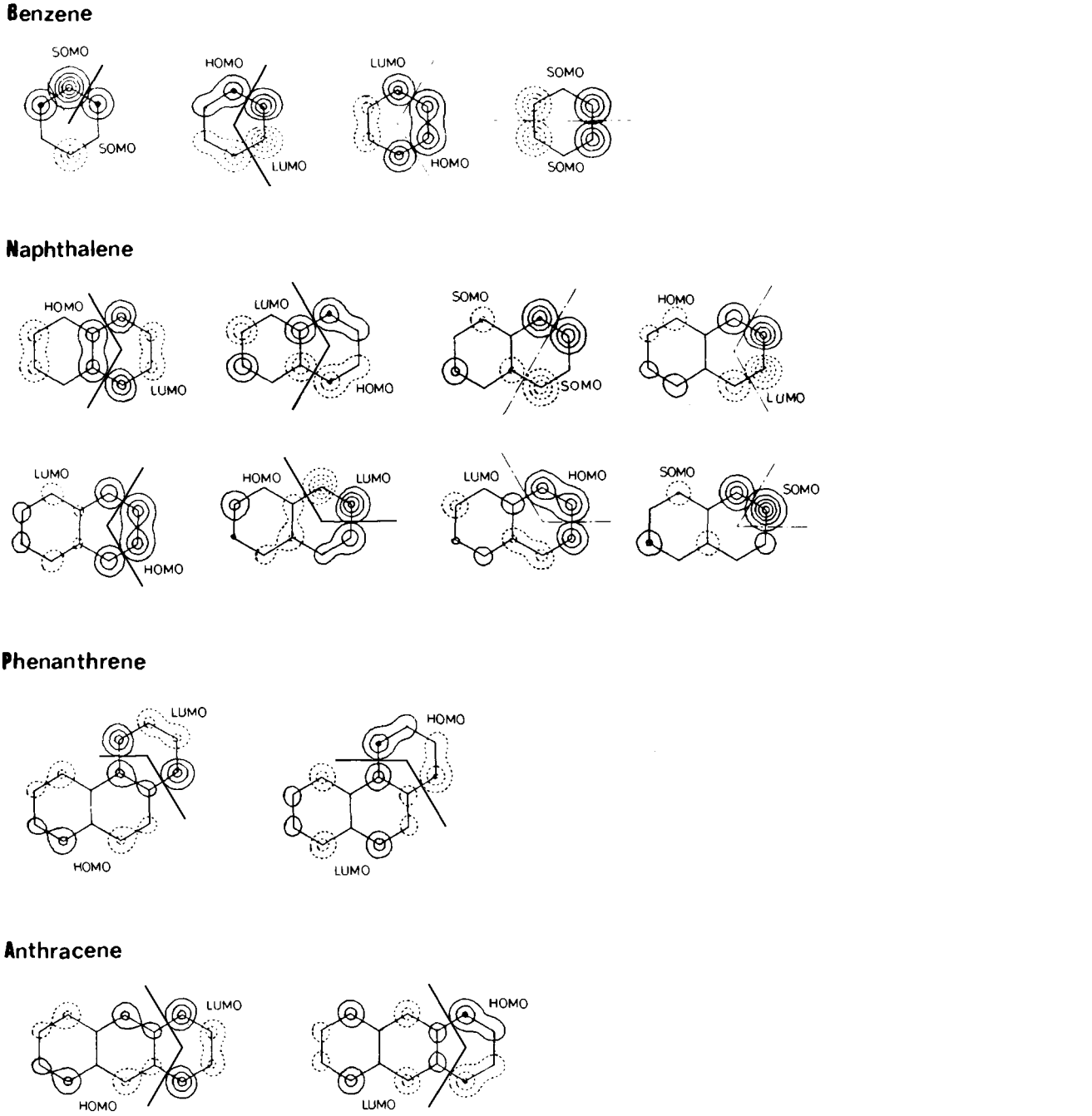
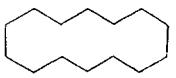


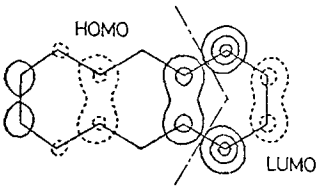
Fig. 4. The HOMO-LUMO phase relationship upon random division of aromatic hydrocarbons (SOMO = singly occupied MO of a radical).

It is well known that anthracene occasionally undergoes reactions similar to additions to olefins.

According to *Hückel*'s (4n + 2)-rule, mentioned previously, the anthracene molecule has 14π electrons and fulfils the stability condition for "aromaticity". Actually, if one considers a molecule of anthracene with the two internal bridging bonds deleted,



it is readily seen that the HOMO and the LUMO of each fragment overlap in an in-phase manner at both of the junctions:



In this way, it is clear that the two bonds which were deleted exert an unfavorable influence on the aromaticity. Such an influence bears a close resemblance to that of impurity scattering of the wave of a free electron moving in a metal crystal.

This discussion seems to be a digression but, as a matter of fact, it is related to the crucial question as to how an electron delocalizes in a molecule. As will be mentioned later, *Anderson*[56] solved the question of how an electron localizes in a random system. In a molecule, there are potential barriers between atoms which must be overcome when certain conditions are satisfied, in order for an electron to move freely around it. Although the question of how valence electrons delocalize in a molecule may not yet have been solved satisfactorily for nonfixed nuclear configurations, the in-phase relationship of the HOMO and the LUMO at the junctions of the two molecular fragments seems to be at least one of the important conditions for the intramolecular delocalization of electrons.

Generally speaking, electron delocalization gives rise to stabilization due to "conjugation", which is an old concept in chemistry. If so, similar stabilization mechanisms must be detected in systems other than aromatic compounds. The discussion of this delocalization stabilization at the transition state or along the reaction path is nothing other than the reactivity theory discussed previously. The term "delocalizability" was attached to the reactivity indices we derived[10], and our reactivity theory itself was sometimes called the "delocalization approach"[14]. Various sorts of "hyperconjugation" can be explained in the same manner. Stabilization due to homoaromaticity or the bicycloaromaticity of *Goldstein*[57], the stability of spirocycles, pericycles[58], of the "laticycles" and "longicycles" of *Goldstein* and *Hoffmann*[59], that of the spirarenes of *Hoffmann* and *Imamura*[60], and so on are all comprehensible as examples of stabilization due to delocalization between HOMO and LUMO, although other explanations may also be possible.

One might ask to what extent such a qualitative consideration is reliable. In many cases, however, a considerably accurate nonempirical determination of the stable conformation of hydrocarbon molecules[61,62] results in a conclusion qualitatively not much different from expectations based on the simple orbital interaction argument mentioned here.

Chemical Reaction Pathways

It has already been pointed out that the detailed mechanism of a chemical reaction along the reaction path can be discussed on the basis of the orbital interaction argument. For this purpose, however, it is necessary that the problem of how the chemical reaction path is determined be solved. The evaluation of the route of a chemical reaction and its rate in terms of the potential energy surface is performed using a statistical-mechanical formulation established by *Eyring*[63]. Many other papers appeared in which the rate expression was derived wave-mechanically using the potential energy function. In addition, the problem of obtaining the trajectory of a given chemical reaction with a given initial condition was treated by *Karplus*[64].

The center line of the reaction path, so to speak, the idealized reaction coordinate—which I called the "intrinsic reaction coordinate" (IRC)[65]—seemed to have been, rather strangely, not specifically defined until then. For that reason, I began with the general mathematical equation which determines the driving force[34,66,67]. Although my papers themselves were possibly not very original, they later turned out to develop in a very interesting direction[68–74], and opened up the method of calculating the quasistatic change of nuclear configuration of the reacting system starting from the transition state and proceeding to a stable equilibrium point[66]. I termed the method of automatic determination of the molecular deformation accompanying a chemical reaction, "reaction ergodography"[34,67]. This method was applied to a few specific examples by *Kato* and I[67], and by *Morokuma*[72,73]: abstraction and substitution of methane hydrogen by hydrogen atoms[67], nucleophilic substitution of methane hydrogen by hydride anions[72], and isomerization of methyl isocyanide to acetonitrile[73]. All of these are very simple reactions, but there seems to be no principal difficulties in extending the applicability to larger systems. Once the IRC was determined in this way, the driving force of a chemical reaction was analyzed on the basis of the orbital interaction argument[66].

In a reacting system with no angular momentum it is possible to obtain the IRC by the use of a space-fixed Cartesian coordinate system. All of the calculated examples mentioned previously belong to this case. However, in a reaction in which rotational motion exists, it is necessary to discuss the IRC after separating the nuclear configuration space from the rotational motion[74–77]. For this purpose it is essential to derive the general classical Hamiltonian of the reacting systems and then to separate the internal motion, which is determined only by the internal coordinates. The nuclear configuration space thus separated

out is, in general, a Riemann space. The classical Lagrangian form obtained in this process of constructing the Hamiltonian is used to derive the IRC equation for the case of rotational motion. It is thus understood that the rotational motion of the reacting system generally causes a deviation from the IRC[74].

Once the method of determining unique reaction pathways is available, the next problem we are concerned with is to see if the pathways calculated can be interpreted in terms of frontier orbital interactions. A method referred to as "interaction frontier orbitals" or "hybrid molecular orbitals" has been developed very recently by *Fujimoto* and I in order, once and for all, to provide a lucid scheme of frontier orbital interactions with the accuracy of nonempirical calculations[78–80]. By properly including contributions from MO's other than the HOMO and the LUMO, we realized in terms of orbital diagrams how ingenious the empirically established chemical concepts—"reaction sites" and "functional groups"— and the empirical concept of reaction pathways could be.

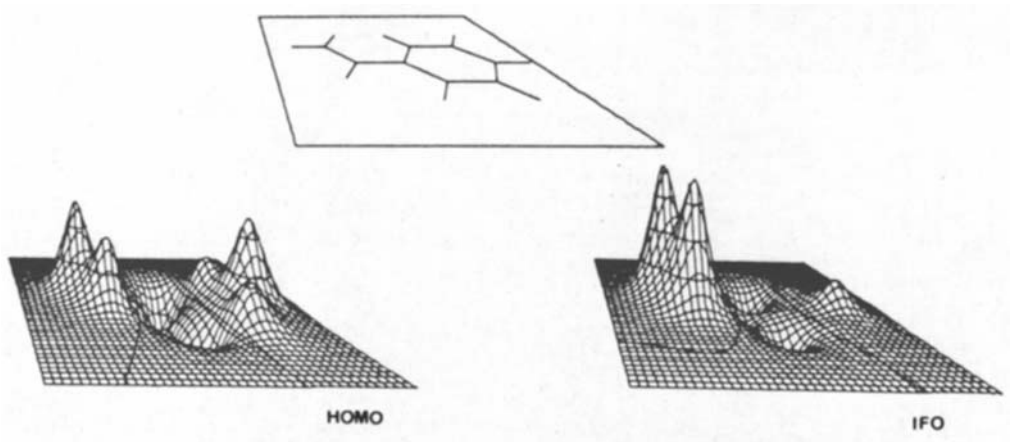


Fig. 5. Comparison of the HOMO and the IFO (interaction frontier orbital) for protonation of styrene.

Figure 5 compares the HOMO of styrene and its interaction frontier orbital (IFO) for protonation of the olefinic double bond. The latter is seen to be localized very efficiently at the site of chemical interaction. The double bond is evidently the functional unit in this case.

Innovation of the frontier orbital concept will hopefully be continued by young scientists to make it useful for one of our ultimate targets: theoretical design of molecules and chemical reactions.

Frontier Orbitals in Related Fields

Theoretical treatments of the properties of solid crystals, or chemisorption on a solid surface appear hitherto to have been almost a monopolistic domain of physics. But the orbital pattern technique has also advanced gradually into this field.

The "cluster approach"[81,82], in which a portion of the metal crystal in the form of a cluster of atoms is selected and its catalytic action or other properties investigated, has contributed to the development of the orbital pattern approach, because purely physical methods can hardly be applied to such large systems. It is expected that if clusters of various sizes and shapes are studied, the characteristic feature of their HOMO's (high-lying occupied MO's) and LUMO's (low-lying unoccupied MO's), the nature of chemisorption and catalytic action, the mode of surface chemical reactions, and several related subjects of interest will be able to be investigated theoretically.

As is the case with molecular interactions in normal chemical reactions, only the HOMO and LUMO bands lying in the range of several electron volts around the Fermi level can participate in the adsorption of molecules and surface reactions on solid crystals. You may recollect here that in the BCS (Bardeen-Cooper-Schrieffer) theory of superconductivity, too, only the HOMO's and LUMO's in close proximity to the Fermi surface are involved in the formation of electron pairs as the result of interactions with lattice vibrations. For solid catalysts the discrimination of particular orbitals and electrons from the others makes the situation much easier.

Consider a system composed of a regular repetition of a molecular unit, for instance, a one-dimensional high-polymer chain or a one-dimensional lattice, in which a certain perturbation is imposed at a definite location. Sometimes it is convenient to discuss the influence of this perturbation by transforming the orbitals belonging to the HOMO band to construct the orbitals localized at this site. One such technique was proposed by *Tanaka, Yamabe* and I[83]. This method is expected, in principle, to be applicable to a discussion of such "local" problems as the adsorption of a molecule on the two-dimensional surface of catalysts, surface reactions, and related matters. This approach may be a little more "chemical" than the method using the function of local density of states[84] or similar functions, in that the former can be used for the discussion of the reactivity of molecules on a catalyst surface in terms of the phase relationship of localized orbitals.

Low-dimensional semiconductors and some superconductors have also been the objects of application of the orbital argument. In these studies, the dimerization of S_2N_2 to S_4N_4[85] and its polymerization to high-polymeric $(SN)_x$[86] were discussed, and the energy band structure of the $(SN)_x$ polymer chain analyzed to investigate the stable nuclear arrangement and the mode of inter-chain interactions[87].

The modern techniques used in solid-state physics to interpret the interesting characteristic behavior of noncrystalline materials, in particular of amorphous materials in which the nuclear arrangements are not regular, are certainly striking. *Anderson* showed generally that in a random lattice system electron localization should take place[56]. *Mott* in his 1977 Nobel lecture, stated that he thought it the first prize awarded for the study of amorphous materials, and answered the question, "How can a localized electron become conducting?" using the concept of "hopping". Here, too, the HOMO-LUMO interaction—in this case the consideration of spin is essential—plays an important role.

In a few words I want to refer to the importance of virtual orbitals. The LUMO, which has held a key position in the orbital arguments hitherto discussed, is the virtual orbital which an external electron is considered to occupy if captured by a molecule to form an anion. Virtual orbitals always play an essential part in producing metastable states of molecules by electron capture[88]. To discuss such problems generally *Tachibana et al.*[89] systematized the theory of resonant states from the standpoint of the complex eigenvalue problem. The idea of resonant states will play a principal role in chemical reactions, particularly in high-energy reactions, which will be developed more in the future.

Prospects

In this article I have presented a series of recent results, largely from the studies carried out by our group, and have ventured to make those things the object of my talk which appear promising, but which are not yet completely established. In doing this my intention has been to stimulate the efforts of many younger chemists by specifying what fields I believe to be promising for the future.

In my opinion, quantum mechanics can make two different contributions to chemistry. Firstly, it permits nonempirical comprehension of experimental results. However, we should not overlook another important aspect: the promotion of empirical chemistry from the theoretical side. Here, also, reliable theoretical foundations and computational methods are required. The conclusions provided by theoretical considerations should be little affected by the degree of sophistication of the approximations used.

On the other hand, the contributions, made by theoreticians to the second aspect mentioned, in which predictions surpassing experimental accuracy are possible by very accurate calculations, are for the present limited to a very few, extremely simple molecules. In order to accomplish this objective for ordinary chemical problems, it is sometimes necessary to provide qualitative theories which can be used even by experimental chemists. If one can contribute nothing to chemistry without carrying out accurate calculations for each specific problem, one cannot be said to be making optimal use of quantum mechanics. It is certainly most favorable when the underlying concepts are as close to chemical experience as possible, but this sphere of experience is steadily expanding. Quantum chemistry has thus the task of furnishing useful concepts on a theoretical basis and of making them available to the experimental chemist.

Even the same atoms of the same element in different molecules show different behavior: the chemical symbol H seems to signify atoms of a completely different nature. In chemistry, this terrible individuality should never be avoided by "averaging", and, moreover, innumerable combinations of such atoms form the subject of chemical research, where it is not the "whole assembly of compounds of different kinds but each individual kind of compound" that is of chemical interest. As a consequence of this formidable complexity, chemistry inevitably depends on analogy through experience. This is in a sense the fate allotted to chemistry, and the source of its great difference from physics. Quantum chemistry, too, in so far that it is chemistry, is required to be useful in promoting experimental chemistry.

Acknowledgements

Lastly, I want to take this opportunity of mentioning the names of many members of my research group who have walked the same road as mine since my first paper (1952) on quantum chemistry, particularly Drs. *T. Yonezawa, C. Nagata, H. Kato, A. Imamura, K. Morokuma, T. Yamabe,* and *H. Fujimoto,* and also the scientists mentioned in the text who made contributions in opening up new aspects in this field. Among them, Prof. *T. Yonezawa* was helpful in performing calculations in our 1952 paper. It is to be mentioned with appreciation that the attractive title "frontier orbitals" of my lecture originated from the terminology I adopted in that paper upon the suggestion of Prof. *H. Shingu,* who as an organic chemist participated by classifying the relevant experimental results. Furthermore, many other young collaborators are now distinguishing themselves in other important fields of chemistry, which, however, have not been the object of this article.

It was the late Prof. *Yoshio Tanaka* of the University of Tokyo and Prof. *Masao Horio* of Kyoto University who recognized the significance of my early work. I owe such theoretical work, which I was able to carry out in the Faculty of Engineering, Kyoto University and in the Department of Fuel Chemistry, to the encouragement and kind attentiveness of Prof. *Shinjiro Kodama,* who fostered the Department. What is more, it was the late Prof. *Gen-itsu Kita,* my life-teacher and founder of the Department, who stimulated me to enter chemistry, one of the most attractive and promising fields of science. For all of these people no words of gratitude can be sufficient to express my thanks.

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From Isocyanides *via* Four-Component Condensations to Antibiotic Syntheses**

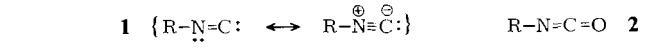
By Ivar Ugi*

In memoriam Otto Bayer

The four-component condensation of amines and carbonyl compounds with isocyanides[***] and suitable acid components (water, thiosulfuric acid, hydrogen selenide, hydrogen azide, cyanic acid, thiocyanic acid, carboxylic acids, methyl hydrogen carbonate) to form α-amino acid derivatives was discovered in 1959. This reaction principle shares some features with the Strecker synthesis and the Passerini reaction. The four-component condensation affords easy and effective one-pot synthesis of complex molecules from simple building blocks. Only in recent years, however, have the preparative advantages of the four-component condensation been exploited by numerous authors in the synthesis of diverse natural products and related compounds, although many of the possibilities opened by this principle were recognized more than two decades ago. In this progress report some instructive syntheses of various antibiotics are reviewed. The design of each of these syntheses involves a four-component condensation as key step, by means of which lengthy sequences of reactions are avoided, which otherwise would be required to achieve the synthetic goal.

1. Introduction

The essential reactions of the simple functional groups have long been known. Almost all basic types of organic compounds were thoroughly studied by the classical organic chemists in the last century. The isocyanides **1** and the isocyanates **2**, close chemical relatives, are among the exceptions. For a long time, relatively little research was carried out on either class of compounds, and it was comparatively late that they received the attention they deserve.



1 **2**

The chemistry of the isocyanates began to gather momentum in the late thirties, when *Otto Bayer* initiated an intense exploration of these hitherto practically neglected compounds. With great vision he then created the conceptional foundations of polyurethane technology: this is based on isocyanate chemistry and the polyaddition principle, recognized by *Bayer* as a means of synthesizing macromolecules. *Bayer* thus triggered a unique development to which the isocyanates owe their present eminent scientific, technological, and commercial importance.

Systematic investigation of the isocyanides[1] began about 1960. Most of the isocyanide reactions on which synthetic methods are based were discovered only in the last decade. Examples are the reactions of the α-metalated isocyanides by *Schöllkopf et al.*[2], *van Leusen*'s "TosMIC chemistry"[3], and the aldehyde-ketone syntheses of *Walborski et al.*[4].

In the meantime, isocyanides have become a household word in preparative organic chemistry, although it is not long ago that they were seen as exotic compounds, useless for synthetic purposes. Just a few years ago the reviewer of an article about preparative uses of isocyanides[5] called it "intellectually rewarding"—probably a well-meant and courteous circumscription for "an academic topic without practical consequences". However, the isocyanides have finally come into their own as preparative reagents, as demonstrated by the syntheses reviewed in this article.

Why was it more than a hundred years from the discovery of the isocyanides[1a,6] to the true dawning of their chemistry, although many interesting reactions have long been known or predictable? The main reason was probably the lack of preparative access to pure isocyanides in high yield until the advent of modern methods for their preparation[1b]. The classical isocyanide syntheses—the "carbylamine reaction" of *A. W. Hofmann*[7] and the synthesis of isocyanides by alkylation of silver cyanide according to *Lieke*[6] and *Gautier*[8]—are of little use for the preparation of pure isocyanides. The efficient modern syntheses of the isocyanides are based on the dehydration of *N*-monosubstituted formamides. As early as 1867 *Gautier*[9] attempted to convert the latter into isocyanides by allowing them to react with P_4O_{10}. He did not succeed, because he had overlooked the fact that isocyanides are acid sensitive. The synthesis of isocyanides from *N*-monosubstituted formamides proceeds well only when the acid-forming dehydrating agents, such as arenesulfonyl chlorides[10], phosphorus oxychloride[11], sulfonyl chloride[12], or phosgene[13], are used in the presence of bases.

The "phosgene procedure", which is carried out in the presence of triethylamine, dimethylaniline or aqueous bases[14], is generally the method of choice. The phosgene can be substituted by "diphosgene"[15], which has recently

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[***] Previously, isocyanides were almost always referred to as isonitriles. However, according to IUPAC Rule C-833.1 only the name "isocyanides" is permissible.

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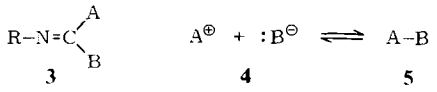
become readily available[16]. Diprotonated carbonyldiimidazole is useful as a substitute for phosgene in the preparation of base-sensitive isocyanides in small quantities[17].

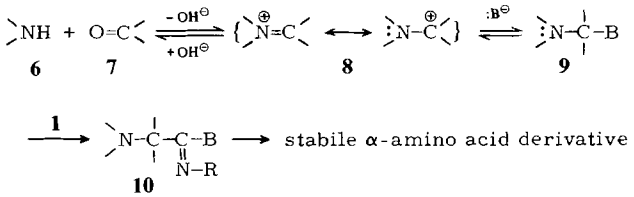
The formal divalency of the isocyanide carbon atom is responsible for the peculiarities of isocyanide chemistry. The formation of isocyanides is generally accompanied by conversion of tetravalent into divalent carbon, and most reactions of the isocyanides begin with an α-addition **1**→**3**, *i.e.* conversion of a divalent into a tetravalent carbon atom[1].

The pronounced ability of isocyanides to participate in multicomponent reactions is based on the α-addition of electrophiles and nucleophiles which may be involved in the equilibrium **4** ⇌ **5**.



3 **4** **5**

The majority of the classical multicomponent reactions, such as the Mannich condensation and the Strecker synthesis, are α-amino-alkylations[18]. These proceed *via* iminium ions, highly reactive electrophiles capable of existing as "equilibrium species" in media of low acidity. Thus, they qualify as reaction partners for the acid-sensitive isocyanides.

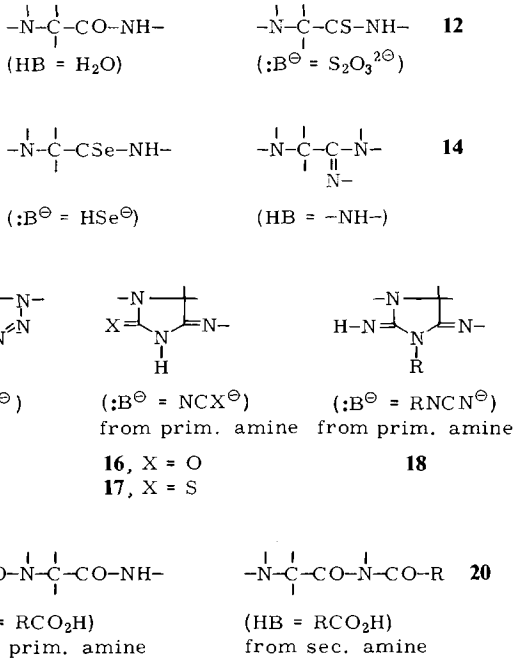


6 **7** **8** **9** **1** **10**

There are many nucleophiles ($:B^{\ominus}$) whose α-aminoalkylation, **8**→**9**, is reversible. Reversible α-aminoalkylation systems are generally able to react with isocyanides **1** to form labile α-adducts **10** which undergo spontaneous rearrangement to afford stable α-amino acid derivatives[1d, 19–29].

We use the term four-component condensation[22] for those reactions whose products are formed *via* α-addition of an iminium ion and a nucleophile to an isocyanide, followed by a secondary reaction of the α-adduct formed (cf. **21** + **22** + **23** + **24**). As a synthetic principle, four component condensation affords simple one-pot syntheses of a large variety of compounds, whose syntheses by alternative methods would generally require complex, multistep sequences of synthetic reactions[21]. Formulas **11**–**20** represent those classes of compounds available *via* four-component condensation of ammonia, primary and secondary amines, or hydrazine derivatives, and carbonyl compounds with isocyanides and suitable acidic components or their anions, such as water, thiosulfate, hydrogen selenide, dimethylamine[23], azide, cyanate, thiocyanate, carboxylic acids, and monoalkyl carbonates[1d, 21].

The nature of the products is primarily determined by the acidic component HB or its anion $:B^{\ominus}$. However, in the case of some acidic components (see **19** and **20**) the essential structural features of the product also depend on whether the amine component is primary or secondary.



11 (HB = H_2O) **12** ($:B^{\ominus}$ = $S_2O_3^{2\ominus}$)

13 ($:B^{\ominus}$ = $HSe^{\ominus}$) **14** (HB = –NH–)

($:B^{\ominus}$ = $N_3^{\ominus}$) **15**

($:B^{\ominus}$ = $NCX^{\ominus}$) from prim. amine **16**, X = O **17**, X = S

($:B^{\ominus}$ = $RNCN^{\ominus}$) from prim. amine **18**

19 (HB = RCO_2H) from prim. amine **20** (HB = RCO_2H) from sec. amine

The first four-component condensations, involving rather simple components, were carried out in methanol, and their products were isolated without recourse to chromatographic methods. Since these experiments generally resulted in high yields of products without significant detection of by-products, the initial impression was that all reversible side reactions were suppressed by a large thermodynamic driving force, and that hardly any irreversible side reactions occur[21]. Model experiments carried out later in which reactants and reaction conditions were widely varied indicated, however, that four-component condensations do indeed compete with a variety of irreversible side reactions which impair their yield[29]. Over the years, however, it was also found that the competing side reactions can, as a rule, be avoided with a good understanding of the reacting system. For a given four-component condensation, it is usually possible to find—through systematic model experiments—some conditions under which an excellent yield can be obtained. This optimum yield is, however, only obtained when the optimum conditions—including the precise concentrations of the reactants and additives[25]—are carefully observed. Most of the four-component condensations proceed in 75–95% yield, if the Schiff base of the enamine of the amine and carbonyl components, as well as the acid component are allowed to react in a 1 : 1 molar ratio in stirred concentrated methanolic solution with the isocyanide at 0 °C[1d, 27].

Based on the available data[25], mechanistic steps of third or higher order do not take part in the reaction mechanism of four-component condensations. Under a wide variety of conditions the mechanism of the four-component condensation is a complex system of consecutive and parallel first and second order reactions. Those steps in which only the amine, carbonyl and acid component participate are reversible, whereas those steps in which the isocyanide takes part are irreversible[25].

The scope and limitations of the four-component condensation and its reaction mechanism, as well as its de-

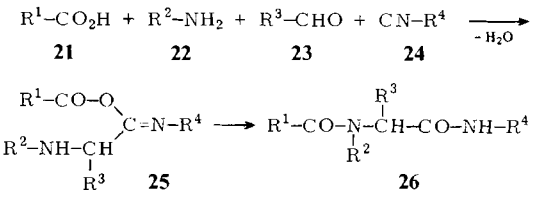
pendence on reaction conditions[1d,25,27] were, however, first studied systematically after 1962, when I moved from Universität München to the Wissenschaftliches Hauptlaboratorium of Bayer AG at Leverkusen, which was then under the directorship of *Otto Bayer*. His active interest in this topic, his critical participation in discussions, his constructive ideas, and the intellectually stimulating atmosphere of the laboratory, which was strongly determined by *Bayer*'s personality, not only profoundly influenced, helped, and stimulated the investigations of my research group in Leverkusen until 1968, but also far beyond: this period at Leverkusen is also the origin of other major research topics and areas of interest of the present author. They all began as auxiliary projects, corollaries and "fallout" from the four-component condensation, and its most obvious and important application, the synthesis of peptides[27-29]. This in turn is the source of the preparative[30] and theoretical investigations on stereochemistry[31-38] and chirality[34,35], as well as the later work on permutation isomers[36] and their mutual interconversions[37]. These led *via* hyperchirality[38] to the theory of the chemical identity group, a unified perspective of static and dynamic stereochemistry as a whole[39].

The computer assisted efforts towards understanding the mechanism of the four-component condensation[25], in order to make best use of it synthetically, led *Günter Kaufhold* and myself to design and implement the Leverkusen peptide synthesis planning program[40,41], an intellectual ancestor of the theory of the *BE*- and *R*-matrices[42], and to develop the concepts, algorithms, and computer programs for the deductive solution of a great variety of chemical problems[43], which are based on this unified theory of constitutional chemistry.

Last, but not least, some of our experimental work deserves mention, whose origin and motivation also stems from the four-component condensation: the chemistry of the α-ferrocenylalkylamines and related compounds[44], which serve as chiral auxiliary materials in the synthesis of peptide segments by the four-component condensation[29], the studies on functionalized polymers[45], and the development of new protective groups for the four-component synthesis of peptide segments. Later, this work led to the development of protective groups that can be selectively cleaved by Co^{I} phthalocyanine in neutral solution: these are used in peptide and oligonucleotide synthesis[47]. Even our work on phosphorus chemistry[48] is a consequence of the four-component condensations, *via* the related stereochemical studies[37].

2. Four-Component Condensation of Carboxylic Acids and Primary Amines with Aldehydes and Isocyanides

The reaction of primary amines **22** and aldehydes **23**—or better still, the Schiff bases of **22** and **23**—with carboxylic acids **21** and isocyanides **24** leads *via* the α-adducts **25** to the α-acylamino carboxylic acid amides **26**[1d,21,25-29] From a mechanistic standpoint (cf. [36]), and according to the essential structural features of the products **26**, this type of four-component condensation may be viewed as a "cross-breed of the α-aminoalkylation[18] with the Passerini reaction[1c].

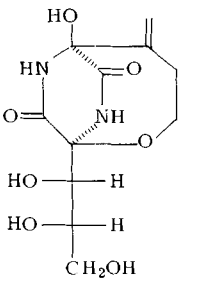


This variant of four-component condensation opens up new ways of synthesizing many natural products and their analogs, including numerous antibiotics and their precursors.

Various syntheses of antibiotics have recently been reported in which a four-component condensation of the last mentioned type plays a key role. These syntheses, with the exception of syntheses of peptide antibiotics, are reviewed in this article.

3. Bicyclomycin

Bicyclomycin, **27**, an antibiotic which is active against gram negative bacteria, has been isolated in crystalline form from culture filtrates of *Streptomyces sapporonensis*[49]. Its unusual structure, as elucidated by X-ray crystallography[50], and its promising antibiotic profile[51] make its synthesis a challenge[52,53].



27

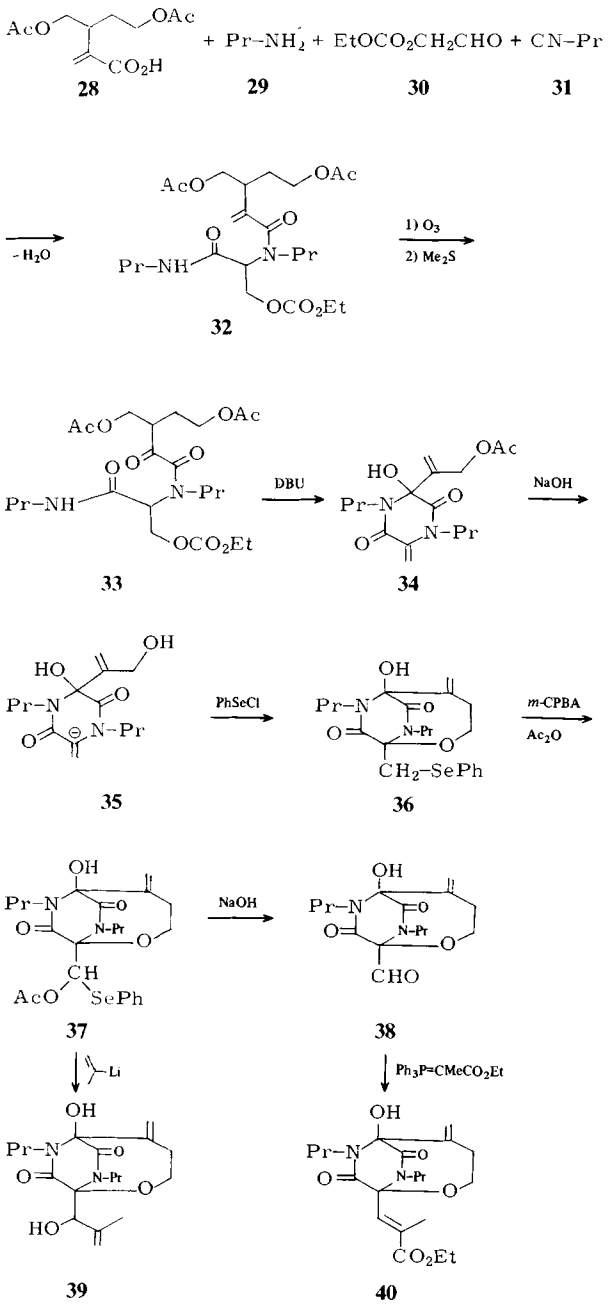
Fukuyama, Robins, and *Sachleben*[52] have recently performed an impressive synthesis of **39** and **40**, which can be seen as a model and a precursor of a total synthesis of **27**. The formation of **32** by four-component condensation of **28** to **31** to give the polyfunctional compound **32** is a key step (DBU = diazabicyclo[5.4.0]undecene[54], *m*-CPBA = *m*-chlorobenzoic acid).

According to *Fukuyama et al.*[52] this approach provides an access not only to bicyclomycin, but also to a variety of analogous compounds. Their structure is predetermined by the educts of the initial four-component condensation.

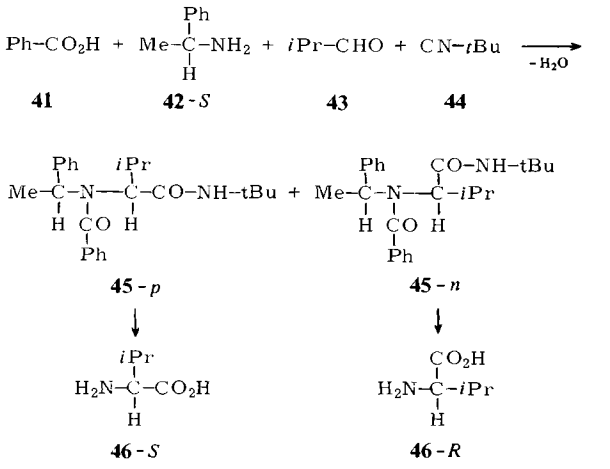
4. Asymmetrically-Induced Four-Component Condensation and the Synthesis of Furanomycin

As a model reaction for the asymmetrically-induced synthesis[35,55] of chiral amino acid and peptide derivatives, the formation of **45-*p*** and **45-*n*** by four-component condensation of **41** to **44** has been thoroughly studied[1d,25,27].

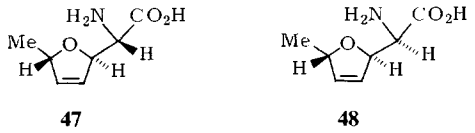
The ratio Q_{pn}[56] of the products **45-*p*** and **45-*n*** depends strongly on the reaction conditions[25,27]. Computer-assisted analysis of Q_{pn} as a function of the concentrations of



the starting materials **41** to **43** in methanol at 0 °C revealed that four competing pairs of corresponding reactions, *i.e.* pairs of reactions whose products and transition states are stereoisomeric, are involved. These four pairs of reactions differ with respect to their formal reaction order[25], and correspond to four competing reaction mechanisms. The observable overall stereoselectivity results from the concentration-dependent relative contribution of the individual pairs of corresponding reactions[31,32], each of which has its characteristic concentration-independent "intrinsic" stereoselectivity[41]. The relative yield of a given stereoisomer is maximized if conditions prevail under which that pair of corresponding reactions dominates whose "intrinsic stereoselectivity" most favors this stereoisomer. Moreover, the contributions of the unfavorable pairs of corresponding reactions must be minimized.

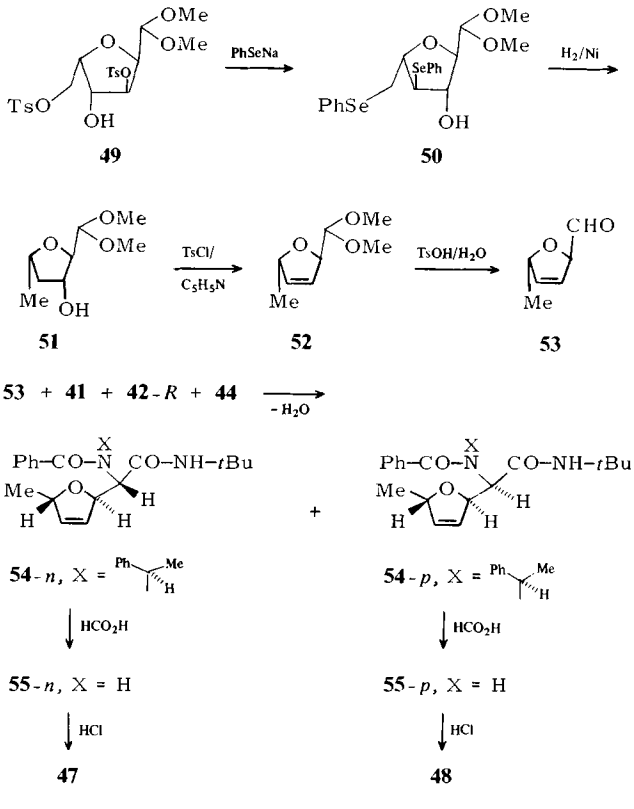


The results of the above model experiments were used by *Joullié et al.*[57b] in their synthesis of (+)-furanomycin **47** and related compounds. *Katagiri et al.*[58] isolated the



antibiotic furanomycin **47** from culture filtrates of *Streptomyces threomyceticus* and assigned to it the structure **48** based on spectroscopic data. Later, on the basis of NMR data[57-59] and preparative results[57,60], which were obtained partly *via* four-component condensations, the corrected structure, **47**, or (+)-furanomycin was obtained.

An elegant stereoselective four-component synthesis of (+)-furanomycin by *Joullie et al.*[57b], that was carried out in several variations, starts from D-glucose, which is converted into the aldehyde **53** *via* **49**. The four-component

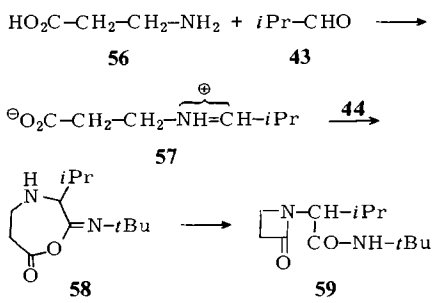


condensation of **53** with **41**, (*R*)-α-phenylamine **42-*R***, and *tert*-butyl isocyanide **44** yields **54-*n*** and **54-*p***. Acidolysis of **54-*n*** with formic acid leads to **55-*n***, whose hydrolysis affords **47**.

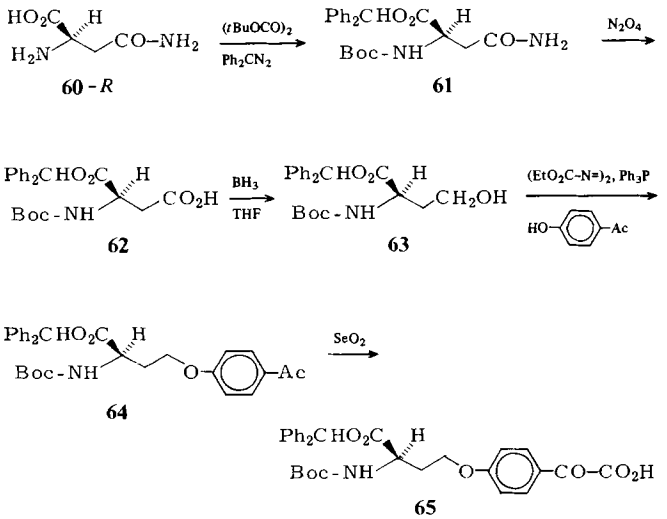
5. Nocardicin and Analogs

The recent literature indicates that interest in the β-lactams is still increasing[61], because of their outstanding antibiotic properties and few undesirable side effects. Even monocyclic β-lactams with noteworthy antibiotic activity have been found. In 1976 some Japanese authors[62,63] isolated nocardicin A, **75**, the first monocyclic β-lactam with potentially useful antibacterial properties. Together with six analogs, the nocardicins B—G[64], it occurs in the culture broths of *Nocardia uniformis*.

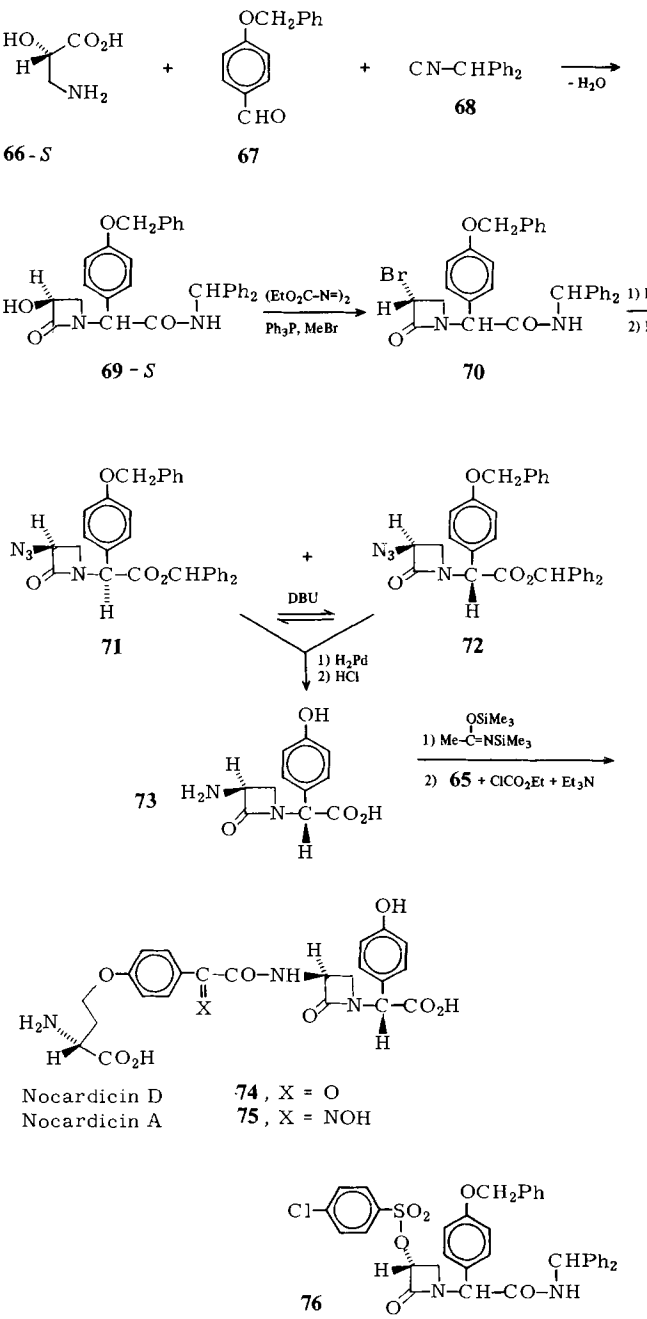
The formation of four-membered rings by cyclization of acyclic precursors is generally impeded by Baeyer strain and conformationnal effects; hence, formation of β-lactams from β-amino acids is not easy[65]. However, conversion of β-amino acids into β-lactams by four-component condensation proceeds smoothly, as a rule, in very good yields[1d,26,66]. For example, the difunctional **56** reacts smoothly with **43** and **44** in methanol to form **59**[1d,26].



In the synthesis of β-lactams by four-component condensation a seven-membered ring (cf. **58**) is formed, which closes relatively easily. The β-lactam system (cf. **59**) is obtained from the α-adduct by a secondary transannular *O,N*-acyl transfer.



Nocardicin A, **75**, has already been synthesized by conventional methods[67]. The advantages offered by four-component condensation for the synthesis of β-lactams were used impressively by *Isenring* and *Hofheinz*[68] at the Hoffmann-La Roche laboratories in their synthesis of 21

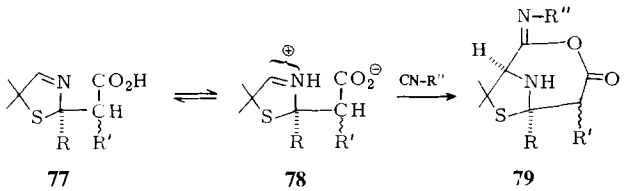


nocardicin analogs[68a]. As examples, we select the syntheses of nocardicin D, **74**, and A, **75**. The acid **65**, required for the last step, is first prepared from D-asparagine **60-*R***. An important step following the four-component condensation to **69-*S*** is the conversion of **71** into **72** by diazabicycloundecane[54]. **69-*R***, obtained analogously to **69-*S***, reacts *via* **76** to afford **71** and **72**.

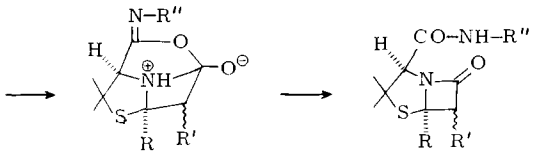
In this context the four component synthesis of 3-aminonocardinic acid by *Hatanaka et al.*[69] also deserves to be mentioned.

6. Penam Derivatives

The first preliminary studies towards the synthesis of penicillin derivatives by four-component condensation were carried out more than 20 years ago by *Ugi* and *Wischhöfer*[70]. 3-Thiazoline derivatives **78**, prepared by Asinger condensation[71] of β-oxoesters, ammonia and α-mercaptoisobutyraldehyde, and subsequent ester hydrolysis, were allowed to react with isocyanides in the two-phase system water/petroleum ether to afford the penam derivatives, **81**. Despite the general lability of penam derivatives, the products **81** could be purified by sublimation *in vacuo*. This four-component condensation proceeds *via* the bicyclic α-adduct **79**, in which, due to strain, the seven-membered ring can only be *cis*-annelated. Thus, in **81** the β-lactam moiety and the carbamoyl group must be *cis*-related.



77 **78** **79**



80 **81**

a, R = H, R′ = Me; **b**, R = Me, R′ = H

Using a similar route *Sjöberg*[72] obtained the amide of a stereoisomer of penicillin G, but in very low overall yield, because formation of the required 3-thiazoline derivative by Asinger condensation did not proceed satisfactorily.

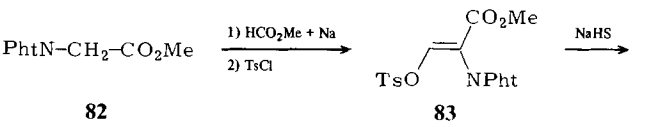
Schutz and *Ugi*[73] found the route **82** → **86** to 3-thiazoline derivatives, which can be converted into 6-aminopenam derivatives or their stereoisomers. Here, as also in the synthesis of cepham derivatives (see Section 8), the thienolate **84** is the key intermediate (Pht = phthaloyl).

Demethylation of **86** by LiI in dimethylformamide and pyridine gives **87**, whose four-component condensation with **44** in water/dioxane produces **88**. According to NMR results the asymmetric C-atoms in the β-lactam moiety of **88** have the same configurational relationship as in the natural penicillins.

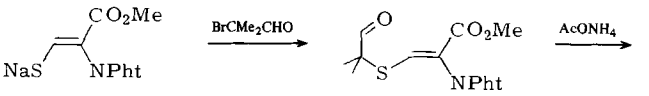
The conversion of **88** into penicillin G would require substitution of the phthalimido by a phenylacetamido group, as well as that of the *trans*-carbamoyl by a *cis*-carboxy group. All these operations are possible, but their execution on the penam system requires further model experiments. Analogous considerations apply to the synthesis of the cephalosporins (Section 8).

7. Carbapenem Derivatives

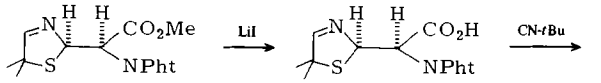
Thienamycin **90** and related carbapenem derivatives are distinguished by outstanding antibiotic activity[74]; accordingly, their syntheses deserve particular attention[75].



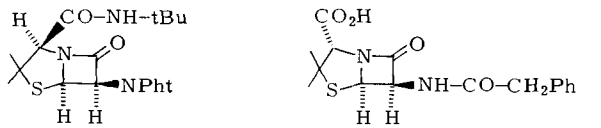
82 **83**



84 **85**

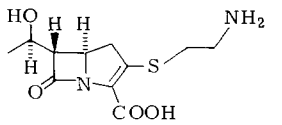


86 **87**

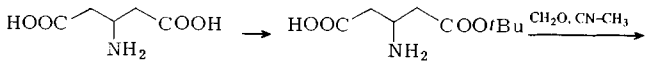


88 **89**

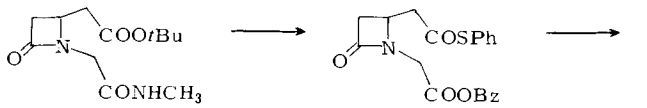
Hatanaka et al.[76] recently reported a synthesis of **96**. In its relative brevity, this synthesis sets new standards for the carbapenem field. The key step is a four-component con-



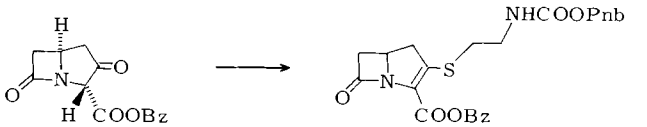
90



91 **92**



93 **94**



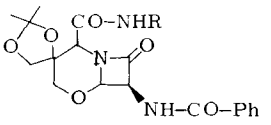
95 **96**

densation of **92** with formaldehyde and methyl isocyanide yielding **93**. A modified Dieckmann condensation **94** → **95** and subsequent condensation of **95** with protected cysteamine leads to **96** (Pnb = *p*-nitrobenzyl, Bz = benzyl).

The authors indicate that an analogous total synthesis of the thienamycin **90** is well underway.

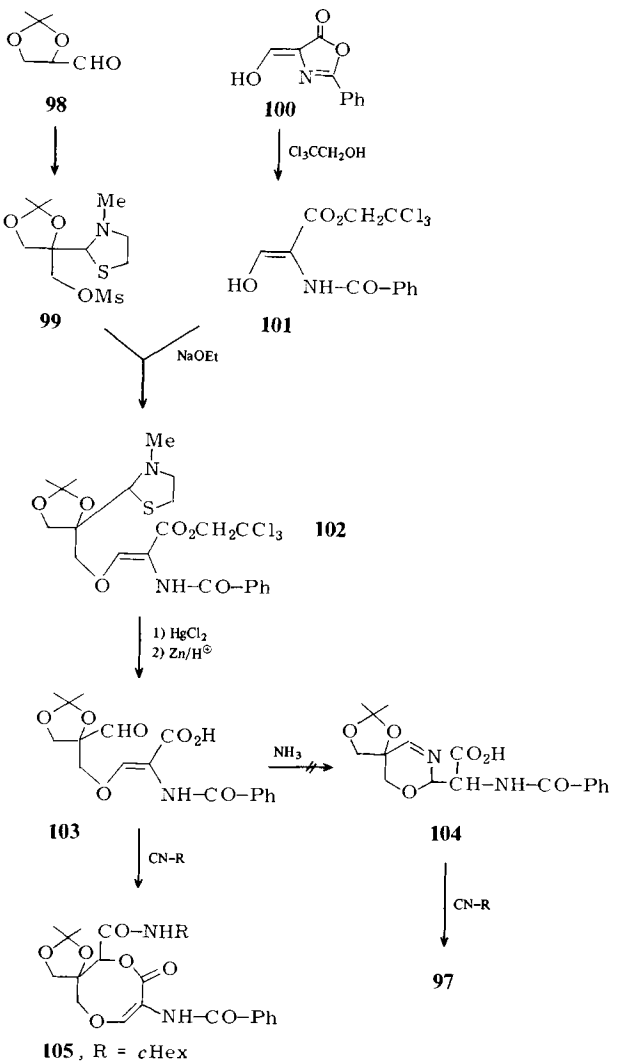
8. Cepham Derivatives and Related Compounds

Just et al.[77,78] attempted the synthesis of the oxacepham derivatives **97** as outlined below. This synthesis was planned as a model for analogous syntheses of cepham derivatives, and its conceptual design is ingenious and convincing.

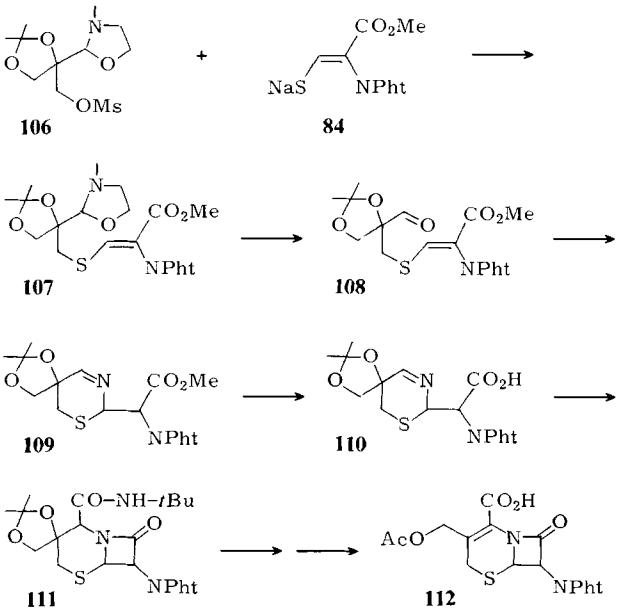


97, R = Et, *c*Hex

The synthesis starts from mannitol diacetonide, from which the glyceraldehyde acetonide **98** is obtained by oxidative glycol cleavage. The latter is converted into **99** by condensation with formaldehyde, subsequent protection of the aldehyde function with *N*-methyl cysteamine and, finally, reaction with methanesulfonyl chloride. The 4-hydroxymethylene-5-oxazolone **100** and trichloroethanol react to give **101**, whose sodium enolate reacts with **99**, yielding **102**. The labile aldehyde **103** is obtained by reductive cleavage of the trichloroethyl group and deblocking the aldehyde group by mercury(II) chloride. Aldehyde **103** was allowed to react *in situ* with ammonia and isocyanides in the hope that it would form a dihydroxazine derivative **104**, whose four-component condensation with an isocyanide ought to yield **97**. Instead, a Passerini reaction[1c] takes place between **103** and the isocyanide to form **105**[78].



Presumably discouraged by this result of their model study, *Just et al.*[78] seem to have abandond their planned synthesis of cepham derivatives. Their synthetic concept is by no means unrealistic, and after minor modification could well be realized (see **106**—**111**). After the successful synthesis of some penam derivatives we[79] took note of the concept of *Just et al.*[77,78] profiting considerably from their ideas and results. The thioenolate **84**, which had already proved its value in the penam synthesis[73], was allowed to react with the mesylate **106**, a reaction already described by *Just et al.*[77] in 1973. Treatment of the resulting product,



107, with aqueous acetic acid yields the aldehyde **108**, and when a slow stream of ammonia is passed over a stirred solution of this in tetrahydrofuran at 0 °C, the tetrahydrothiazine derivative **109** is formed: from this, **110** is obtained by demethylation. Its reaction with *tert*-butyl isocyanide leads to the cepham derivative **111**, whose essential configurational relations correspond to those of the natural cephalosporins, according to NMR data. It is intended to convert **111** or some analog obtained by four-component condensation into a cephalosporin **112**.

9. Perspectives

Although the four-component condensation, its versatility and most of its preparative advantages have been known for more than two decades[19], practitioners of organic synthesis have not made much use of it until recently. In many areas the required "supporting chemistry" has only been developed in recent years. For example, twenty years ago it was known that stereoselective four-component condensations are, in principle, useful for the synthesis of peptide segments[29]; however, syntheses of this type

did not become practicable until chiral α-ferrocenylalkylamines became accessible *via* the "Mannich condensation with exchanged roles"[44c], and subsequent resolution of the enantiomers with the aid of (−)-diisopropylidene-2-oxo-L-gulonic acid[80] became feasible. The facile recovery of the chiral amine components of such peptide syntheses[81] also had to be solved. Furthermore, were it not for the non-linear stereoselectivity effect of destructively selective reactions[33,35,83], discovered in 1975, stereochemically pure peptide segments could hardly have been synthesized by four-component condensation. The development of novel protective and auxiliary groups which can be removed by Co^{I} supernucleophiles[47] may also prove to be essential.

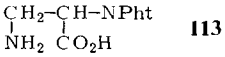
For some synthetic goals, four-component condensation has given rise to a shift in emphasis. In the synthesis of β-lactam antibiotics by conventional methods, construction of the β-lactam moiety is the central issue. However, in syntheses using the four-component condensation, the β-lactam part of an antibiotic only receives attention because of its lability towards acids and bases.

Progress in understanding the mechanism of the four-component condensation and its side reactions[29] will extend its applications. Studies of this type may lead to the selection of reaction conditions under which the formation of by-products is practically avoided, and the desired product—and if need be one of several stereoisomers—is obtained in maximum yield and purity.

It is foreseeable that the scope and efficiency of four-component condensations will grow with the development of new reagents and techniques. The following comments on the syntheses of antibiotics reviewed in this progress report may illustrate and support this statement.

Alkylamines and alkyl isocyanides, whose alkyl group can be selectively cleaved under mild conditions may, for example, be useful for the synthesis of bicyclomycin **27** and related compounds.

Straightforward syntheses of the nocardicins (*e.g.* **74**, **75**) would be possible if a derivative of L-α,β-diaminopropionic acid with a suitably protected α-amino group, such as **113**, where available.



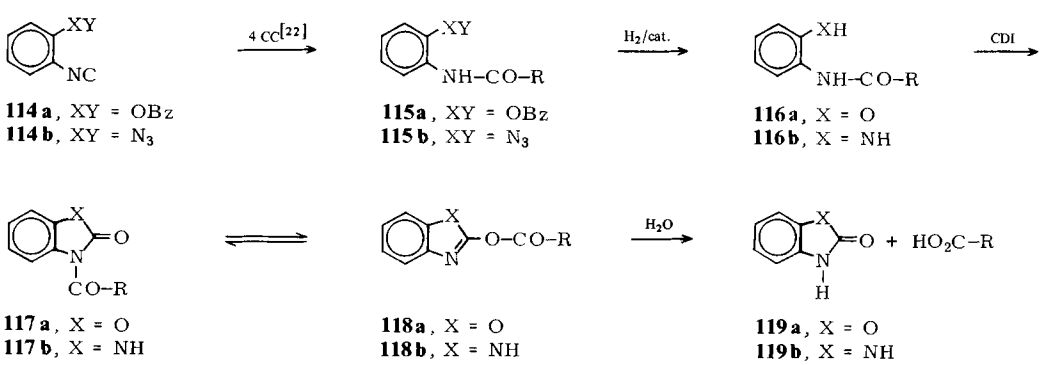
113

Since azidoacetaldehyde has recently become available[82], the synthesis of **113** should be feasible from a condensation product of the following four-components: *tert*-butyl monophthalate, azidoacetaldehyde, (*R*)-α-ferrocenyl-isobutylamine[44b], and an isocyanide with a selectively cleavable carbamoyl group.

The synthesis of furanomycin **47** and related compounds can probably be improved by using a chiral α-ferrocenylalkylamine as the asymmetrically inducing amine component, and by combining a productively stereoselective four-component condensation with a destructively stereoselective cleavage of the chiral auxiliary group[83].

The synthesis of β-lactam antibiotics by four-component condensation requires the conversion of the carboxylic acid amide group originating from the isocyanide component into a free carboxy group. Neither the cleavage of amides by nitrosation, used by *Isenring* and *Hofheinz*[68] in their synthesis of nocardicin nor the imidochloride method used by *Hatanaka et al.*[76] is universally applicable. Accordingly, the cleavability of the *o*-hydroxy- and *o*-aminoanilides **116a** and **116b**, respectively, by acylating derivatives of carbonic acid, such as carbonyldiimidazole (CDI)[84], is leading to novel β-lactam antibiotic syntheses *via* four-component condensation. *Kametani et al.*[85] have recently demonstrated that the racemate of an (α-branched) β-amino-β′-hydroxycarboxylic acid can be synthesized *via* diastereoselective 1,3-dipolar cycloaddition of a nitrone to some alkyl crotonates, and subsequent hydrogenolysis of the resulting isoxazoline derivative. This could serve as the starting material for a synthesis of racemic thienamycin **90** by a four-component condensation. If a chiral nitrone with powerful asymmetric inducing power were used in an analogous synthesis, a chiral β-amino-β′-hydroxycarboxylic acid would be formed, which in combination with the results of *Hatanaka et al.*[76] and amide cleavage according to **114** → **119** could be the basis of the conceivably most effective synthesis of thienamycin **90**. Since on the one hand it can be anticipated that thiemycin will not be produced microbiologically, and on the other that, because of the particularly favorable profile of this class of substances, one of its derivatives will find a place in the clinic, the thienamycin synthesis outlined could become the most important application of the four-component concensation in the near future.

Progress in isocyanide chemistry is dependent, to some extent, on the development of an "imbedding chemistry" as illustrated by the examples of advances in the area of antibiotics discussed here. Isocyanide chemistry still has ample virgin territory at its frontiers. Further advances will, however, only lead to optimum success if isocyanide chemistry and the rest of organic chemistry are well interfaced.



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Tricyclo[3.3.0.0^{2,8}]octan-3-ones: Photochemically Prepared Building Blocks for Enantiospecific Total Syntheses of Cyclopentanoid Natural Products

By Martin Demuth* and Kurt Schaffner*

Dedicated to Professor Oskar Jeger on the occasion of his 65th anniversary

Bi- and tricyclopentanoid natural products have been in the focus of synthetic interest in recent years. With widely applicable building blocks lacking, most work has been restricted in the past to specific approaches to single racemic target structures. A novel concept is now presented which uses for the first time a simple building block, tricyclo[3.3.0.0^{2,8}]octan-3-one, providing enantiospecific access to diverse cyclopentanoid structures. Tricyclooctanone is obtained in a few steps and in high yield from benzene, *via* the triplet-sensitized oxa-di-π-methane rearrangement of bicyclo[2.2.2]octenone as a photochemical key reaction. Smooth preparations of both enantiomers are possible by resolving the racemic mixture and of the bicyclooctenone. Owing to its structural properties the tricyclooctanone undergoes a wide array of regio- and stereoselective transformations in high yields, in compliance with the expectations for a synthetic key compound of general applicability. The total syntheses of boschnialactone, allodolicholactone, irido- and isoiridomyrmecin, and loganin aglucone 6-acetate provide the first examples of successful applications. Promising entries to coriolin, 6a-carbaprostacyclin and homologs, and 6,11-dehydroestrone complement this review of the potential of tricyclooctanone as a versatile building block for the enantiospecific total synthesis of polycyclopentanoids and related compounds.

1. Introduction

In recent years a remarkable number of natural products has been isolated which belong to the group of compounds containing a cyclopentanoid carbon skeleton. Several of these have proven to possess biological activities of pharmacological interest. This has stimulated interest to prepare such substances synthetically and to meet the methodological challenge of constructing bi- and tricyclopentanoid skeletons, and of achieving selective functionalizations of such systems. The area is relatively undeveloped and has therefore been in the forefront of research interest for several years.

Scheme 1 presents a characteristic selection of intermediates and building blocks which have so far been used in the synthesis of cyclopentanoid compounds. It is evident that, in general, building blocks with a broad range of applications have been lacking and that the synthetic goals have been restricted to racemic end products only—with exception of the single case ⑩, which, with an enantiomeric excess of merely 40%, is still far from satisfactory. In connection with ⑩ it should be noted that the Robinson annelation, which is a highly enantioselective alternative for six-membered ring systems in the presence of chiral bases, is not applicable to five-membered ring systems[17].

As shown by the transformations ① and ②, transannular reactions on eight-membered rings were used to construct bicyclo[3.3.0]octane derivatives[1,2]. The condensation ③[3] of ketoglutaric acid ester was utilized, *e.g.*, with biacetyl (R = CH_3)[4] in the synthesis of (±)-gymnomitrol, and with glyoxal (R = H)[5] for the synthesis of 6a-carbaprostacyclin[6]. A [2+2] ketene addition and subsequent extension of the four-membered ring ④ provided a route to (±)-hirsutene[7]. In far more cases, enones and enediones served as building blocks. Thus, the syntheses of (±)-hirsutene[8] (*via* ⑤[9]), members of the (±)-pentalenolactone group (*via* ⑥[10]), (±)-isocomene[11] (*via* ⑦[12]), (±)-quadrone (*via* ⑧, R = $CHCH_2$[13], R = CH_2CH_2Br[14]), and (±)-coriolin (*via* ⑨[15] and ⑩[16,18]) have been reported.

The examples given in Scheme 1 illustrate the general tendency, which is also shown by numerous other studies[19-23], to concentrate on synthetic approaches, each designed specifically for a single target structure. A more far-reaching concept which evolves from a central key reaction and is applicable to structurally diverse classes of compounds, is represented only by transformation ⑩.

2. The Concept

The following concept is the first to open an enantio*specific* access to the different structural variants of the cyclopentanoid natural products. In addition to this fundamental advantage, the new synthetic approach[24-28] is also superior, over the methods mentioned previously, regarding the flexibility in the set-up of the pattern of substitution. The objective was to prepare a basic set of simple building blocks with structural features which would allow for a multitude of transformations of predictable regio- and stereoselectivity, and for a smooth resolution into *both* enantiomers. The tricyclo[3.3.0.0^{2,8}]octan-3-ones **3** (see Scheme

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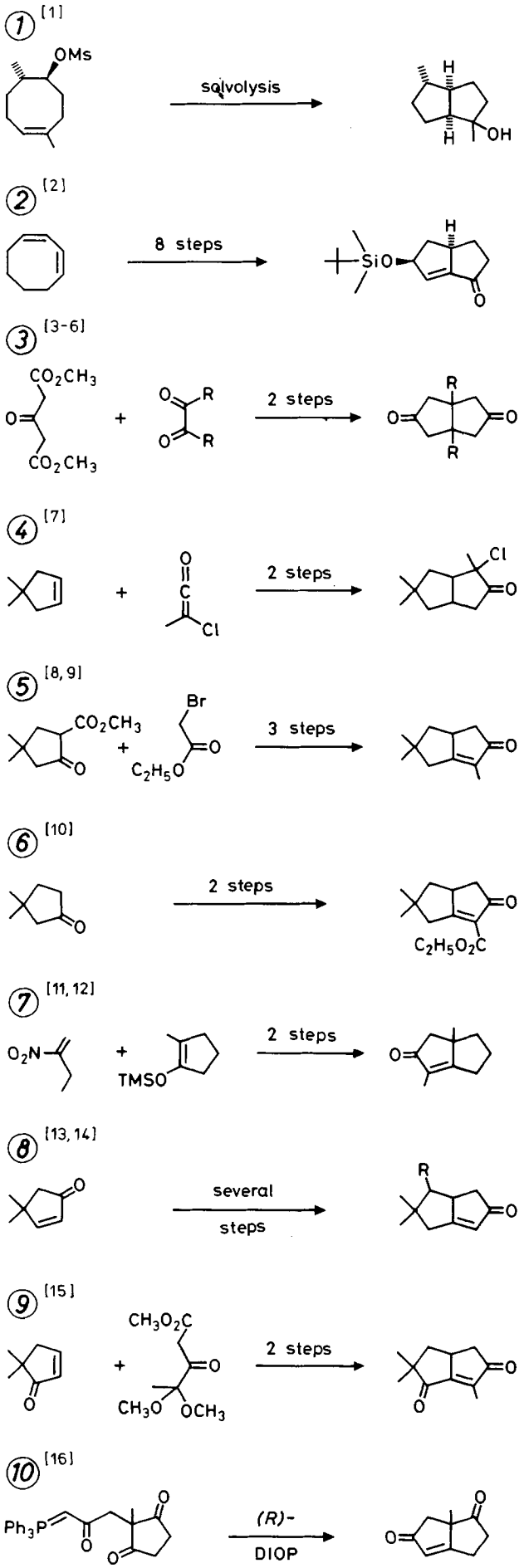
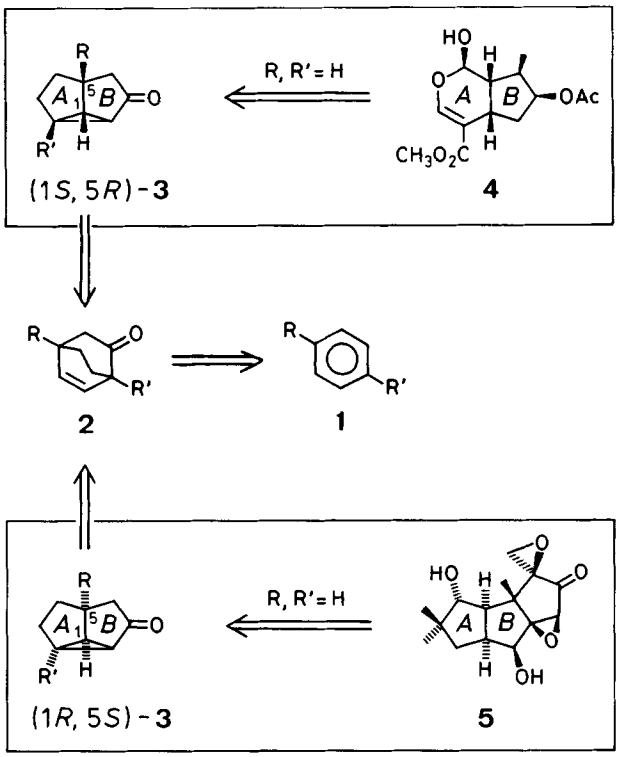


2 and Table 1) will be shown to satisfy these requirements to a large extent. They are readily accessible from the commercially available aromatic starting materials **1**, the key step being the photochemical rearrangement of the β,γ-unsaturated ketones **2**. The tricyclooctanones thus provide an optimum configurational and functional ensemble for economically attractive syntheses of cyclopentanoid target molecules.



Scheme 2. Retrosyntheses using tricyclo[3.3.0.0^{2,8}]octan-3-one **3a**: Loganin aglucone 6-acetate **4** from (1*S*,5*R*)-**3a**, and coriolin **5** from (1*R*,5*S*)-**3a**.

Scheme 2 uses two characteristic examples to illustrate the retrosynthetic analysis of cyclopentanoid natural products, based on the concept so far described.

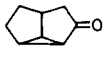
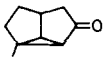
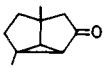
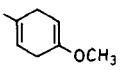
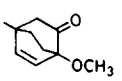
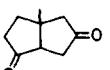
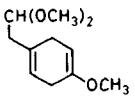
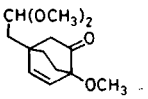
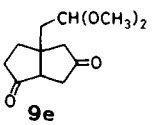
3. Preparation of the Tricyclo[3.3.0.0^{2,8}]octan-3-ones

The tricyclooctanones **3** can be readily produced in high yields from benzene and derivatives thereof. Table 1 compiles the syntheses of compounds of this type which have been carried out so far. Birch reduction of the arenes, and subsequent isomerization of the resulting 1,4-cyclohexadienes **7** *in situ* by heating in the presence of trace amounts of hydroquinone afforded the 1,3-dienes, which were directly added to 2-chloroacrylonitrile. As expected, the Diels-Alder additions to the substituted dienes occurred with high regioselectivity. Only for the synthesis of **3a** was commercially available 1,3-cyclohexadiene **6** used. It was added to acrylonitrile, and the adduct was subsequently chlorinated.

Some time ago, *Givens et al.*[30] described the photochemical rearrangements of **2a** which are quite generally characteristic[34] for those of β,γ-unsaturated ketones: a

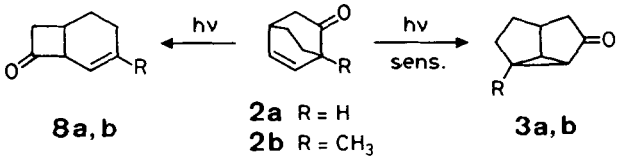
◀ Scheme 1. Selected examples of key steps in syntheses of cyclopentanoid compounds (cf. also Scheme 3). TMS = trimethylsilyl, DIOP = *P,P'*-[2,2-dimethyl-1,3-dioxolane-4,5-bis(methylene)]bis(diphenylphosphane).

Table 1. The Synthesis of **2a–2e**, **3a–3e** and **9d**, **e**.

Educt [a]	Conditions of the Diels-Alder addition and hydrolysis (temperature [°C])	Intermediate **2** [b] yields based on dienes **6** and **7**, resp.	Irradiation conditions	Product [b]
6	[c] [d] [e] (25)	**2a** (64%) [29]	[f]	 **3a** (84%) [30–32]
7b	[g] (150) [e] (120)	**2b** (87%) [25]	[h]	 **3b** (88%) [25]
7c	[g] (135) [i]	**2c** (35%) [j]	[h]	 **3c** (72%)
 **7d**	[g] (90) [k]	 **2d** (69%) [33]	[h]	 **9d** (61%)
 **7e**	[l] (100) [i]	 **2e** (55%) [j]	[h]	 **9e** (84%)

[a] Preparation of **7b—7e** by Birch reduction (Na, NH_3, CH_3OH) in 80—95% yields. [b] Yields of pure products after chromatography on silica gel columns. [c] Acrylonitrile, 2% hydroquinone. [d] PCl_5, pyridine. [e] KOH, dimethyl sulfoxide (DMSO). [f] 1% Acetone solution, 300 nm RUL lamp (Rayonet), quartz flask, room temperature. [g] Chloroacrylonitrile, 1% hydroquinone, toluene. [h] 2% Acetone solution, 0.3 mol equivalents of acetophenone, 340 nm radiation [25], room temperature. [i] Na_2S, KOH, H_2O, C_2H_5OH, reflux. [j] Yields not optimized. [k] Na_2S, H_2O, C_2H_5OH, reflux. [l] Chloroacrylonitrile.

1,3-acyl shift forming the cyclobutanone **8a** on direct excitation, and an oxadi-π-methane rearrangement to **3a** on triplet sensitization.



In extensive studies of other β,γ-unsaturated ketones, the reaction mechanisms of both types of rearrangements have since been elucidated in more detail[35–37]. The 1,3-acyl migration is initiated by photolytic α-cleavage of the ketone to an acyl/allyl diradical which has the option of either regenerating the starting material or recombining in the alternative allylic position and forming the 1,3-shift product. The reaction occurs from the n,π* excited singlet and triplet states of the β,γ-enone, $S_1(n,\pi^*)$ and $T_2(n,\pi^*)$, respectively. In a similarly specific manner the lowest-lying triplet state, $T_1(\pi,\pi^*)$, is responsible for the oxadi-π-methane rearrangement (Fig. 1). In order to selectively secure the formation of the oxadi-π-methane product, excitation to S_1 on direct light absorption by the starting ketone has to be avoided. Also, the triplet energies of enone and sensitizer ought to be carefully adjusted. E_T of the sensitizer should be between T_1 and T_2 of the enone, so that the energy transfer can be directed specifically toward the lower-lying triplet.

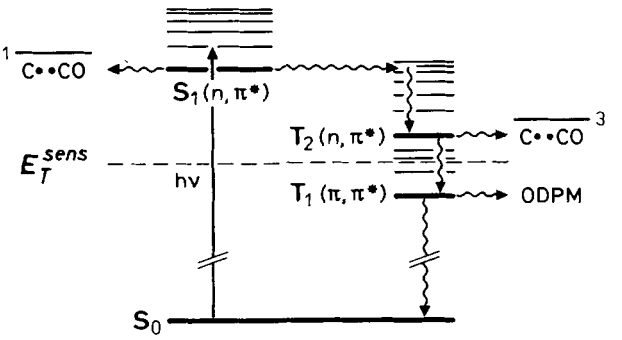


Fig. 1. Energy and excited state diagram of a β,γ-unsaturated ketone, with the optimum range of sensitizer triplet energy (E_T^{sens}) for the oxadi-π-methane rearrangement (ODPM) by selective energy transfer to T_1.

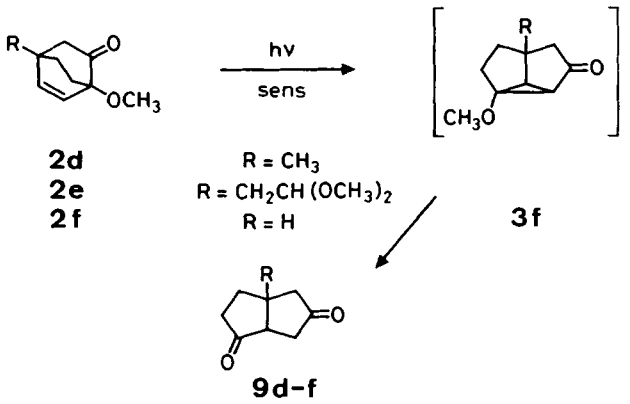
The original low yield of **3a** (34% in acetone upon irradiation with wavelength 254 nm[30]) could be improved considerably by optimizing concentration and irradiation wavelength[25]. Irradiation of 1% solutions of **2a** in acetone at 300 nm, which acts as both solvent and sensitizer, routinely affords **3a** in chemical yields of ≥85%. Only at concentrations above *ca.* 4% of **2a** does the undesired formation of **8a** become noticeable. The dependence of the formation of **8a** on concentration and wavelength (in 1—10% solutions of **2a** and wavelengths of 250—320 nm) points to residual direct absorption, due to insufficient light filtering by acetone, as the cause of the 1,3-shift.

The product distribution in irradiated acetone solutions of the methyl compound **2b** showed a qualitatively similar

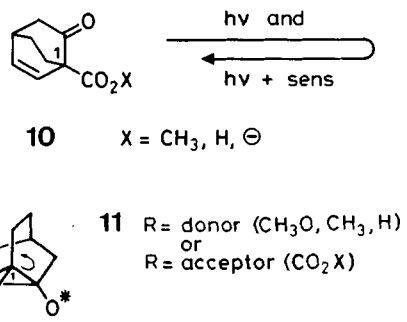
dependence on concentration. However, when the acetone-sensitized conditions which had proved most favorable for the oxadi-π-methane rearrangement of **2a** were applied to **2b**, an already considerable portion of **8b** (18%) was formed. Although the absorption spectra of **2a** and **2b** are essentially superimposable, the 1,3-shift of **2b** could not be suppressed by simply diluting the acetone solution. Only by using acetophenone as a triplet sensitizer and wavelengths $\lambda > 340$ nm could the formation of **8b** be completely avoided. Although this makes an additional purification process necessary, namely a column chromatographic separation of photoproduct and sensitizer, the procedure proved itself to be the more advantageous for all 1-substituted enones (Table 1).

The analogous photochemical behavior of the two enones, **2a** and **2b**, suggests also that the formation of **8b** is due to residual direct absorption. In other words, it is not a consequence of an additional population of the upper triplet of **2b** by acetone sensitization. Rather, the difference in the product formation can be attributed to the 1,3-acyl shift of the α-methylated ketone **2b** being more efficient than that of **2a** (see below).

In the cases of **2d–2f → 9d–9f** a structural variant of the photochemical rearrangement is available which in a very simple way furnishes a bicyclo[3.3.0]octane skeleton possessing experimentally distinguishable ketone groups in the two rings. In the primary product of type **3** the three-membered ring is opened either in a second photochemical step or thermally as a result of the destabilization by the donor-acceptor substitution[38]. Nevertheless, a small amount of the expected product **3f** could be isolated in the previously reported example of **2f**[39], in contrast to the cases of **2d** and **2e**.

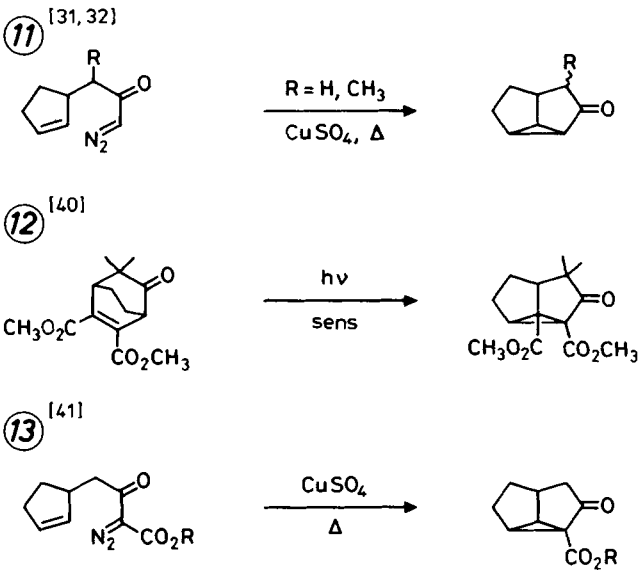


The examples in Table 1 already show the wide scope of the photochemical rearrangement of bicyclo[2.2.2]octenones. Only with the compounds of type **10** were members of this group found which could not be made to react, either by direct excitation ($\lambda = 300$ nm, in chloroform) or by triplet sensitization using acetone, benzene (both on irradiation at $\lambda \leq 300$ nm) or acetophenone (in acetone at $\lambda > 340$ nm). On comparison of these exceptional cases with the ketones **2a–e** it is apparent that photochemical reactivity and inertness parallel qualitatively the electron donor and acceptor properties of the bridgehead substituents in the α-position to the keto group (C1). While an



enhancement of the 1,3-acyl shift efficiency by α-donor substitution, as noted for **2b**, has been described[34] also for 3,4,5,6,7,8-hexahydro-2(1*H*)-naphthalenone (2-octalone) and its 1-methyl and 1,1-dimethyl homologues, investigations with β,γ-enones possessing α-acceptor groups have so far not been reported in the literature. The inhibition of both reaction paths in the case of **10** is possibly due to the electron density at C1 not being adequate enough either for the α-cleavage in the n,π*-excited state of **10**, or for the bond breaking in the intermediate **11** (R = CO_2X; * = ⊙/⊙ or ⊕/⊖) of the oxadi-π-methane rearrangement (cf. Scheme 5).

Tricyclo[3.3.0.$0^{2,8}$]octan-3-one **3a** has already been synthesized using the diazoketone method (Scheme 3, ⑪)[31,32]. This route to **3a** is, however, more costly, and



Scheme 3. Syntheses of tricyclo[3.3.0.$0^{2,8}$]octan-3-one **3a** and its derivatives by other methods.

step ⑪ renders the procedure unsuitable for larger-scale operations. The advantages of our concept become apparent not only when compared with the older synthetic route ⑪, but also even more ostensibly when compared with efforts[41] which have been limited to the more expensive access ⑬ and to a structural variant of smaller synthetic potential. Finally, reaction ⑫ is also worth mentioning, in which *Yates et al.*[40] employed, independently of us, the photochemical oxadi-π-methane rearrangement of bicyclo[2.2.2]octenone derivatives for the synthesis of racemic cedrenes.

4. The Resolution into the Enantiomers

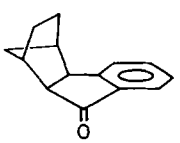
In a first attempt to produce the ketone **3a** in optically active form, the possibility of using an enantioselective energy transfer was investigated. In acetone, the formation of **3a** occurs with the *maximum possible* quantum yield (Φ). As may be seen in Table 2, the Φ values and the rate constants k_q of the triplet energy transfer from the sensitizer to **2a** show the same trend with respect to the sensitizer energy (E_T^{sens}). Both Φ and k_q decrease with decreasing E_T^{sens} values in the range of *ca.* 69—75 kcal·mol^{-1}. The energy transfer from indanone is already clearly slower than diffusion-controlled. One can conclude that E_T of **2a** lies also in this energy range, as do the lowest-lying triplet energies of other β,γ-unsaturated ketones. As a consequence, the energy transfer will be reversible. Although speculative,

Table 2. Rate constants of sensitizer quenching by **2a** and quantum yields of the formation of **3a**; solvent: benzene.

Sensitizer	E_T^{sens} [kcal·mol^{-1}]	λ [nm]	τ^{sens}(exp.) [a] [μs]	k_q [b] [mol·L^{-1}·s^{-1}]	Φ_{max} [c]
Acetone [d]	80 [43]	300			1.0 [e]
1-Indanone	75 [43]	353	1.7	1.0×10^8	
(−)-**12**	74 [f]	>340	20	6.7×10^6 [g]	0.5
Acetophenone	72 [45]	>340			0.3
		353	58	7.5×10^6	
Benzophenone	68 [45]	353	36	7.0×10^6	

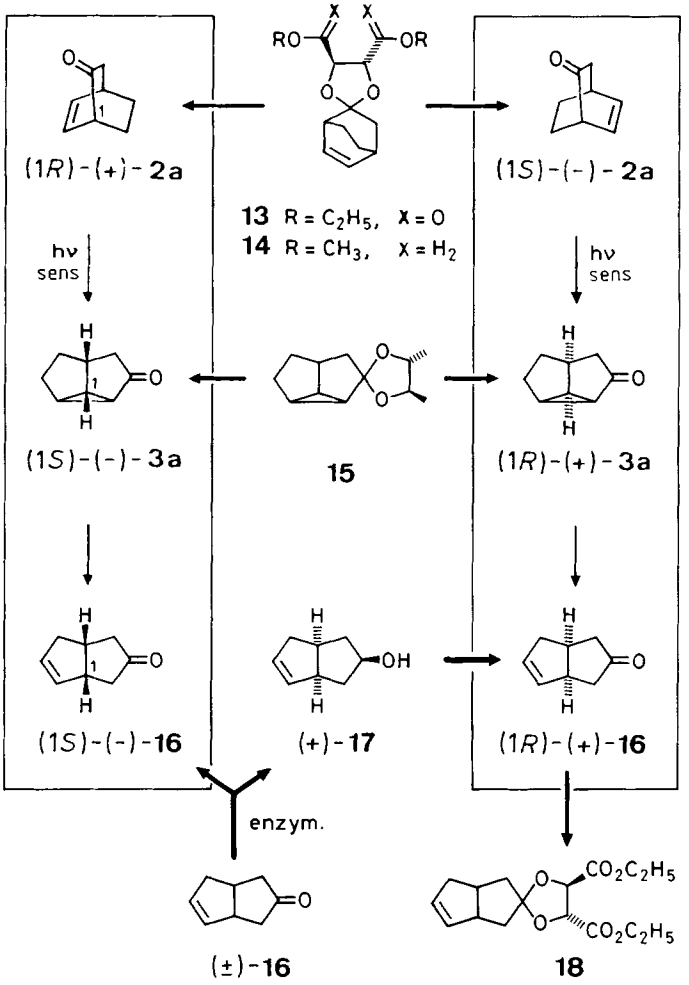
[a] Unpublished laser pulse experiments; for the experimental set-up see [42]. [b] Calculated from the Stern-Volmer slopes ($k_q\cdot\tau^{sens}$). [c] Reciprocal values of the intercept with the Stern-Volmer ordinate [25]. [d] Acetone is also the solvent. [e] Literature value: 0.13 [30]. [f] Estimated value from E_T^{phosph} in ether-isopentane-ethanol (5:5:2) at 77 K [44]. [g] This value may reflect, as a possible additional factor, a larger steric hindrance of the energy transfer than the k_q's of the other sensitizers.

such boundary conditions could be expected to be favorable for an enantioselective transfer from a chiral sensitizer, since control by steric factors should become better noticeable in this situation. However, these expectations were by no means satisfactorily fulfilled when (−)-**12**[44] was used as a sensitizer. The asymmetric induction of the rearrangement of (±)-**2a** was of the same order as in known cases[46] and was insufficient for any practical application. The enantiomeric excess of (−)-**3a** after 7—44% conversion of (±)-**2a** was only 4.5±0.7% in benzene and in ethyl acetate at room temperature, and 10±3% in ethyl acetate at −78 °C. Interestingly, the same order of induction was achieved when (±)-**12** was used to sensitize the rearrangement of **2a** at room temperature in diethyl (+)-tartrate solution.



(-)-12

Satisfactory results were, however, achieved in the production of the pure enantiomers by the resolution of racemic mixtures. This is possible at the stages of the bicyclooctenones **2** and the photoproducts **3** (Scheme 4). The sequence of acetalization, chromatographic separation of the diastereoisomers, and hydrolysis could always be carried out (**13**–**15**) essentially without losses.



Scheme 4. Preparation of the pure enantiomers by reduction of racemic bicyclo[2.2.2]octenone, (±)-**2a**, and tricyclo[3.3.0.0^{2,8}]octan-3-one, (±)-**3a**, and the enantioselective reduction of (±)-**16** with horse liver alcohol dehydrogenase (HLAD). **16** is numbered as in the parent compound **3a**.

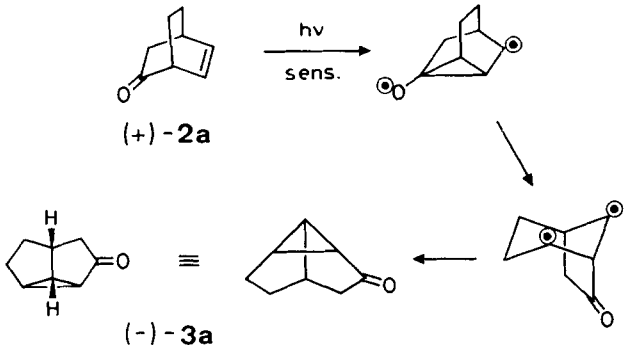
The route *via* the acetal **13** is especially advantageous using the cheapest of the optically active diols, diethyl (+)-tartrate. It also proved itself the best variant with respect to acetalization and chromatographic separation. Thus, (±)-**2a** in the presence of *p*-toluenesulfonic acid in refluxing benzene was quantitatively acetalized to a diastereoisomeric mixture **13**, whereas the transacetalization to **14** with (*S,S*)-(−)-4,5-bis(methoxymethyl)-2,2-dimethyl-1,3-dioxolane[47] reached a conversion of only *ca.* 80%. Chromatography of, *e.g.* 5 g of the mixture **13** using two Lobar C columns (Merck) in series and toluene as eluent, gave 1.9 g of a mixed middle fraction and 1.5 g each of the two components of >98% diastereoisomeric purity. The chromatography columns can be used for several runs.

The alternative route by way of **15** is impaired by the fact that the acetalization of (±)-**3a** with (−)-1,2-butanediol[48] can only be achieved with a conversion of *ca.* 80%. Also, chromatographic separation was not possible beyond a relatively large mixed middle fraction. The method is thus restricted to runs of only a few hundred milligrams.

The absolute configuration of the enantiomeric bicyclooctenones **2a** has been determined previously with sam-

ples obtained by fractional crystallization[49]. The configurational assignment of (+)- and (−)-**3a** is based on the CD Cotton effect of $\Delta\varepsilon_{max}^{306\,nm} = -2.02$ for the (+)-enantiomer, using the octant rule for bicyclo[3.1.0]hexan-2-ones[50].

The stereospecifity of the oxadi-π-methane rearrangement **2**→**3**, as shown by the mechanism given in Scheme 5 and established[37b,c] for other β,γ-unsaturated ketones, was fully confirmed by acetophenone-sensitized irradiations of (+)-**2a** and (−)-**2a** in benzene at room temperature ($\lambda > 340$ nm). The photoproducts, (−)-**3a** and (+)-**3a**, respectively, were formed with complete retention of the enantiomeric purity.



Scheme 5. Stereospecific mechanism of the photochemical oxadi-π-methane rearrangement of (+)-**2a**.

The enzymatic redox system of horse liver alcohol dehydrogenase, HLAD/NAD$^{\oplus}$/ethanol[51], promises to become an important extension of the methods suitable for separation of the enantiomers of this group of compounds. The ketones (±)-**2a**, **b** and (±)-**3a**, **b** could not be reduced enzymatically. In the case of **3** the result is compatible with the likewise negative findings reported[52] for other cyclopropyl ketones and for cyclopropyl aldehydes. However, the bicyclo[3.3.0]octenone (±)-**16**, a product obtained from **3a** in practically quantitative yield (see Section 5, Scheme 6), was reduced by HLAD/NAD$^{\oplus}$ with promising enantioselectivity. When, for example, after a conversion of 48% the reaction was stopped on silica gel and the mixture chromatographed, ketone (−)-**16** and alcohol (+)-**17** were isolated in enriched form, each in not yet optimized yields of 35—40%. The enantiomeric purity of the product of the enzymatic reduction, (+)-**17**, was determined by ^{1}H-NMR spectroscopy using an optically active europium shift reagent. The enantiomeric excess of 65% obtained so far is likewise not optimized. The acetalization of the enriched ketone (+)-**16**—obtained by Jones oxidation of (+)-**17**—with diethyl (+)-tartrate afforded a mixture of the diastereoisomers **18**. However, in contrast to **13**, a gas-chromatographic separation, and thus determination of the diastereomeric mixture, met in this case without success. The *endo*-configuration of the hydroxy group of **17** was assigned on the basis of the hydride mechanism of the enzyme reduction[52]. It is in accord with the sterically equivalent outcome of the $NaBH_4$ reduction of **16** in methanol at 0 °C.

5. Transformations of the Tricyclo[3.3.0.0^{2,8}]octan-3-ones

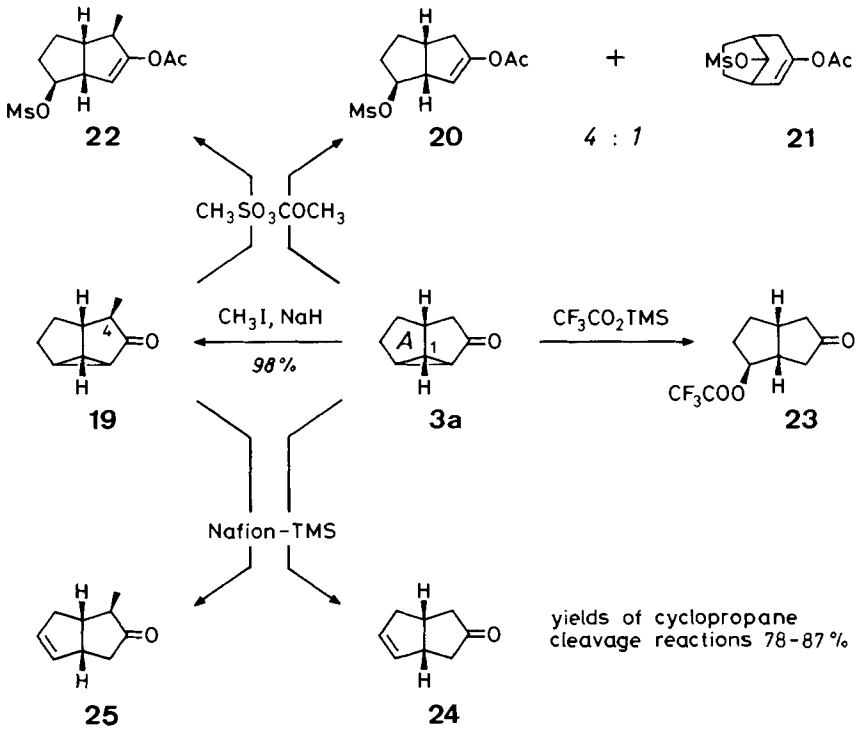
5.1. Functionalization of Ring A of 3a

Electrophilic opening of the three-membered ring of **3a** offers several variants of ready chemical access to the non-oxygenated five-membered ring A. The action of the electrophile can be assisted by a nucleophile which then is employed either in a mixture with the electrophile or in the form of a reagent combining groups with both properties[53,54]. In general, the desired cleavage of the C2—C8 cyclopropane bond is favored by the stereoelectronic control of the reaction. Thus, treatment of **3a** with acetyl methanesulfonate[55] gave product **20** in good yield, but still admixed with the isomer **21** formed by the alternative bond cleavage (Scheme 6[*])[53]. Complete regioselectivity of the reaction was achieved when **3a** was alkylated at C4 to form the homologue **19** with the methyl group exclusively in the *exo*-position (recently another, albeit sterically unselective synthesis of **19** has been described[32].) Reaction of the methyl compound **19** with acetyl methanesulfonate afforded exclusively **22**.

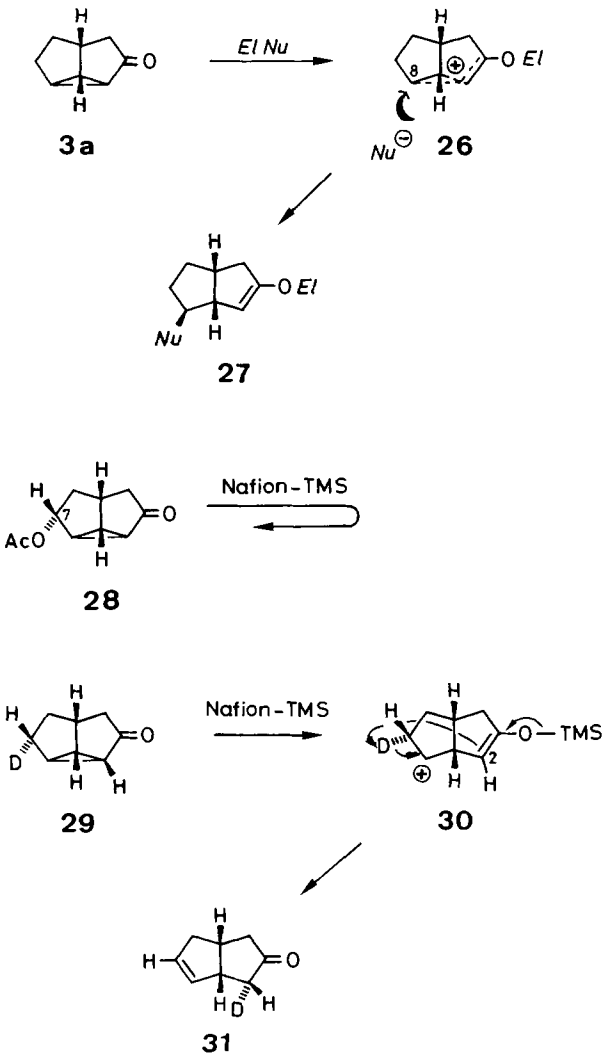
A similarly high stereoselectivity of the cyclopropane opening in the unsubstituted ketone **3a** could only be achieved at the expense of the enolate group which had been preserved in **20** and **22**. Treatment of **3a** with trimethylsilyl trifluoroacetate gave the trifluoroacetoxyketone **23**[54,56], while reaction with trimethylsilyl trifluoromethanesulfonate[56b] in chloroform at room temperature afforded the unsaturated isomeric ketone **24**[26,57]. The nucleophilicity of the trifluoromethanesulfonate is evidently insufficient to add the group to C8. Although analytically quite clean, the yield of this isomerization was substantially reduced upon chromatography. This draw-back could be avoided by the use of Nafion-TMS, a perfluorated trimethylsilyl sulfonate resin[58], in toluene at 80 °C, which yielded pure **24** almost quantitatively. The method can also be used for the isomerization of **19** (→**25**) with similar success[57]. The enone **24** has been prepared previously, employing a considerably less practicable procedure[59].

The sterically very uniform nucleophilic addition to C8 affording compounds such as **20**, **22**, and **23**, points to an S_N2-type mechanism (Scheme 7: **26**). The silyl enol ether **27** could be shown to be a precursor of **23** by gas chromatographic and IR spectroscopic monitoring of the reaction, but it escaped isolation. This is in accord with the previous observation[60] that such functional groups are very readily hydrolyzed to keto groups. The corresponding precursors of **24** and **25** are, however, not cleaved hydrolytically, but rather by way of an intramolecular transfer of the 7-*endo* proton to C2. A number of findings were in agreement with such a mechanism. Thus, the search for an intermediate in the reaction **3a**→**24** was unsuccessful, although the trimethylsilyl enol ether which had been prepared from **24** for comparison purposes, proved sufficiently stable under the conditions used. Also, the cyclopropane cleavage of **3a** with methyl trifluoromethanesulfonate (methyl tri-

[*] The compounds of Schemes 6–13 and 15–17 were prepared in racemic form only.



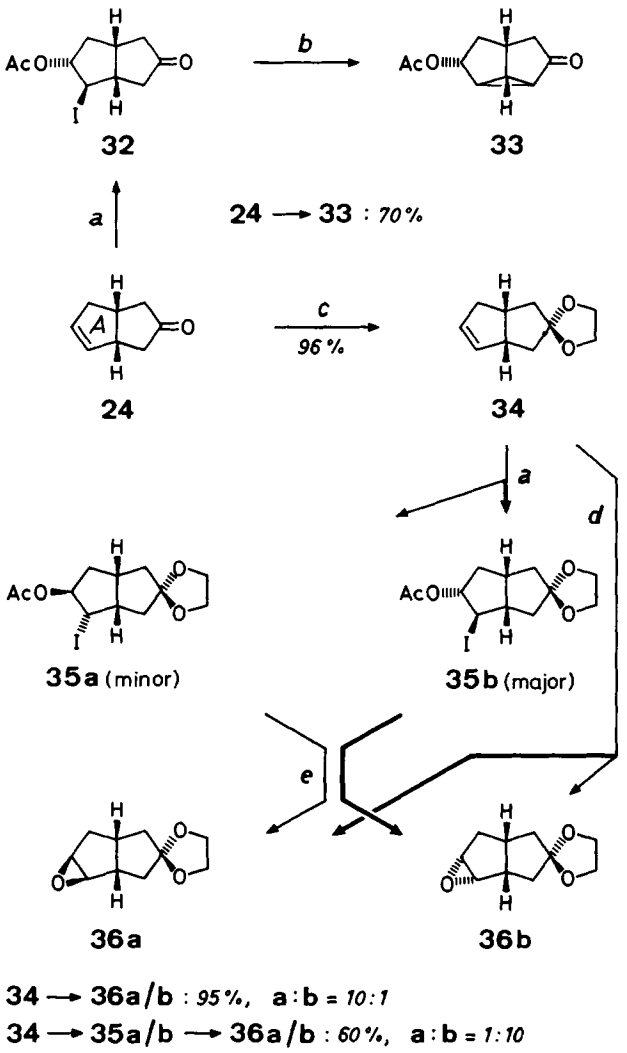
Scheme 6. Functionalization of ring A of **3a**: Cyclopropane cleavage by acetyl methanesulfonate, trimethylsilyl trifluoroacetate, and Nafion-TMS. TMS = trimethylsilyl.



flate) gave exclusively **24**. No methyl enol ether was produced, although it would have been much less susceptible to hydrolysis. Furthermore, the *endo*-7-acetoxyketone **28** remained unreactive under the conditions (Nafion-TMS in toluene at $\geq 80\,^{\circ}C$) under which **3a** was readily isomerized to **19**. This gave the first clue towards the participation of the *endo* proton at C7 in the reaction. Direct evidence for the protolytic cleavage of the enol ether by the intramolecular proton transfer shown in **30** was finally provided as follows: Upon treatment of **29** with Nafion-TMS in toluene at 80 °C the isomerization to **31** amounted to 85% in 6 h. The deuterium was fully incorporated into the 2-*endo* position. Only after an exposure to the reaction conditions for a period of about twice as long was an equilibrium between 2-*endo* and 2-*exo* deuterated stereoisomers established[57].

The Prévost addition of acetyl hypoiodite to the newly formed double bond of **24** occurred with extraordinary regio- and stereoselectivity (Scheme 8), as had already been noted previously with a lactone analogue of **24**[61]. The iodoacetate **32** was obtained in 80—85% yield. Treatment with base restituted the three-membered ring, furnishing **33**. The elimination of hydrogen iodide could be avoided in favor of epoxide formation when the keto group of **24** was acetalized first (→ **34**). The subsequent addition of acetyl hypoiodide occurred with undiminished selectivity. The iodoacetates **35a** and **35b** were formed in a ratio of about 1 : 10. They were directly converted by base into the epoxides **36a** and **36b**, which were readily separated by chromatography. The stereoselectivity of the formation of

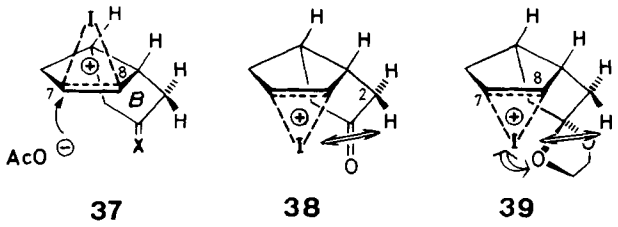
◀ Scheme 7. Mechanisms of the electrophile (*El*)-assisted cyclopropane cleavage with addition of a nucleophile (*Nu*) to C8 and with an intramolecular deuterium transfer from C7 to C2.



Scheme 8. Functionalization of ring A of **3a**: Oxidative additions to the double bond of **24** and restitution of the three-membered ring. *a:* AcOAg, I_2, toluene, 80 °C. *b:* 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), room temperature. *c:* $HC(OCH_3)_3$, $(CH_2OH)_2$, TosOH. *d:* *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 0 °C. *e:* K_2CO_3, CH_3OH.

these products could also be reversed by epoxidizing **34** directly with *m*-chloroperbenzoic acid.

The configuration of the iodoacetate **32** was assigned on the basis of the facile ring closure **32** → **33**, which would not be expected to occur as readily with another configuration at C8[*], as well as model considerations of the course of the Prévost addition. As can be seen from Scheme 9, any addition at the double bond of **24** and **34** from the bottom, *i.e.*, from the side facing ring B (= *endo* attack), is sterically hindered. Thus, *endo* iodonium formation would encounter steric interactions with the *endo* methylene hydrogen at C2 (in **38** and **39**) and, additionally, with the *endo* acetal oxygen (in **39**). In contrast, the *exo* iodonium group **37** is sterically unhindered. The influence exerted by such steric interactions is illustrated by the finding that the substitution of iodine by bromine substantially reduces the stereoselectivity. The *endo* position of the acetoxy group in compounds of type **33** and **35b**, resulting from the *exo* arrangement of the iodonium group, was finally confirmed by an intramolecular ether ring closure (Scheme 15: **61** → **63**) and by the conversion of **35b** into the epoxide **36b**. The configuration of the latter had been established, together with that of **36a**, by ^{1}H-NMR spectroscopy using shift reagents.

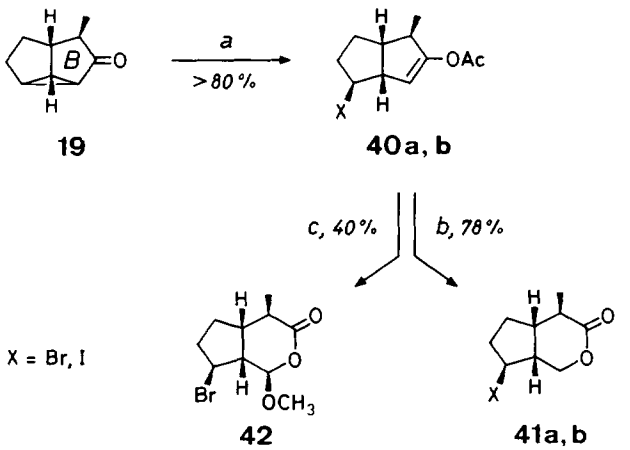


Scheme 9. Stereo- and regioselective control of the Prévost addition of acetyl hypoiodite to **24** and **34** [*].

The preference for position C7 of **37** (X = O and $O(CH_2)_2O$) in the addition of the acetoxy anion can undoubtedly be attributed to the steric shielding of the *endo* side of C8) by the *endo* methylene hydrogen at C2. There remains the question concerning the regio(un)selective attack of the acetoxy anion on **39**. The molecular model does not reveal any significant difference between C7 and C8. The constitution of formula **35a** is therefore arbitrary. Only the *exo* arrangement of the acetoxy group is not in doubt, since the ratio of the epoxides **36a/36b** obtained from the mixture **35a** + **35b** is the inverse of that resulting from direct epoxidation (**34** → **36a**, **b**) by the predominant *exo* attack of the peracid.

5.2. Functionalization of Ring B of 19

The enol acetates of **20** and **22** which had been formed regiospecifically in the cyclopropane opening of **3a** and **19**, respectively (Scheme 6), constituted likely candidates for an extension of ring B into δ-lactones by oxidative cleavage of the double bond. For this purpose, **19** was



Scheme 10. Functionalization of ring B of **19**: Enlargement of the cyclopentenyl acetate to the six-membered lactones **41** and **42**. *a:* $CH_3SO_3COCH_3$, $(CH_3)_4NX$, CH_3CN. *b:* OsO_4, $NaIO_4$, dioxane, H_2O; $NaBH_4$, CH_3OH; HCl. *c:* O_3, CH_3OH, CH_2Cl_2, −78 °C; $NaBH_4$, CH_3OH; HCl; yield not optimized.

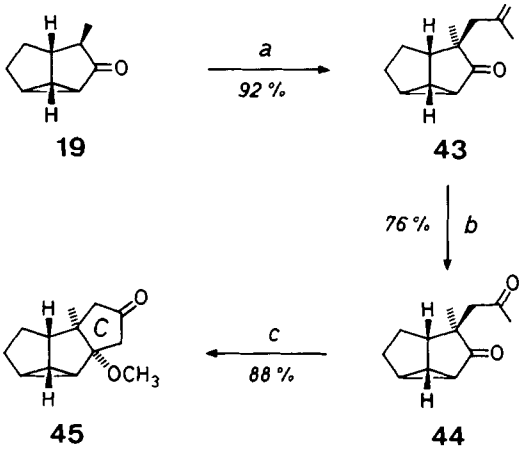
[*] Numbering analogous to that of the precursor **3a**.

converted into the bromo and iodo compounds **40a** and **40b** using acetyl methanesulfonate and the appropriate tetramethylammonium halide (Scheme 10). The double bond was subsequently oxidized by treatment with OsO_4 and $NaIO_4$, the aldehydo function was reduced with $NaBH_4$, and the products were cyclized with acid to the corresponding lactones **41a** and **41b**. The total yield of the sequence **19**→**41** was 69%.

When the bromo compound **40a** was ozonized in methanol, the ozonide was cleaved by the solvent to form a methoxyhydroperoxide[62]. Reduction of the latter to the hemiacetal and acid-catalyzed ring closure gave the methoxylactone **42**.

5.3. Annelation of the Five-Membered Ring to 19

The pronounced steric control of the alkylation at C4 of **3a** could be exploited for the *anti* annelation of a third ring. The product of the first alkylation step, **19**, was converted in high yield into **43** by a second *exo* alkylation using methallyl bromide (Scheme 11). Oxidative cleavage of the CC-double bond of **43** gave the diketone **44**. The base-catalyzed ring closure in the presence of methanol finally afforded uniform tetracyclo[6.3.0.0^{2,4}.0^{3,7}]undecanone, **45**. The uniformity of the end product is due to the spontaneous addition of the alcohol to residual α,β-unsaturated ketone in the crude product mixture. The annelation of ring C was thus completed in three steps and with a total yield of 62%.

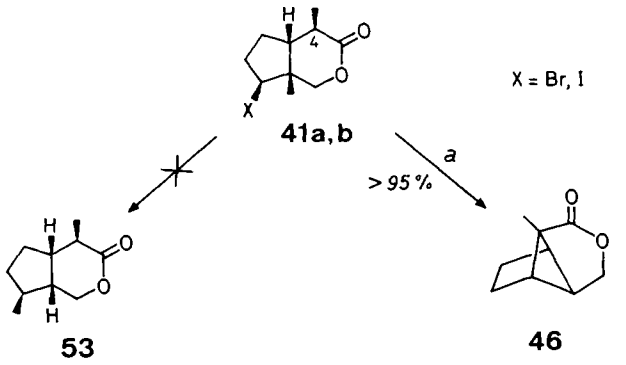


Scheme 11. Construction of the *cis-transoid-cis*-tetracyclic undecane **45** by annelation of the ring C to **19**. *a:* CH_2=$C(CH_3)CH_2Cl$, KBr, *t*BuOK, *t*BuOH, toluene, 80 °C. *b:* OsO_4, $NaIO_4$, tetrahydrofuran (THF), H_2O, room temperature. *c:* *t*BuOK, KOH, CH_3OH, reflux.

6. Applications in Natural Product Syntheses

6.1. Total Syntheses of Boschnialactone, Allodolicholactone, Iridomyrmecin, and Isoiridomyrmecin

The utility of the building block **3a** was tried for the first time in a six-step synthesis of the target molecule racemic isoiridomyrmecin (**53**, Scheme 12), a constituent of the defense secretion of ants. This natural product, which itself is of no practical importance, is a representative of the family of iridoid compounds, many of which exhibit activities of pharmacological interest[63]. The synthesis was initiated in order to confirm, in an early phase of this work, the *exo* steering of the alkylation at C4 of **3a** (→**19**) and of the substitution by nucleophiles at C8 in the cyclopropane cleavage **19**→**22**, **40** (Schemes 6 and 10). The steric course



Scheme 12. Preliminary experiments on the total synthesis of isoiridomyrmecin **53** from (±)-**3a** *via* **19** and **41a**, **b**. *a:* $(CH_3)_2CuLi$ or $(CH_3)_3ZnLi$.

of these reactions—which was expected on the basis of model considerations and supported by spectroscopic evidence from products such as **19**, **22**, and **40**—was finally established by an X-ray diffraction analysis of the bromolactone **41a** (Fig. 2)[26,64].

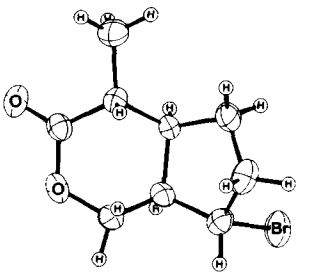
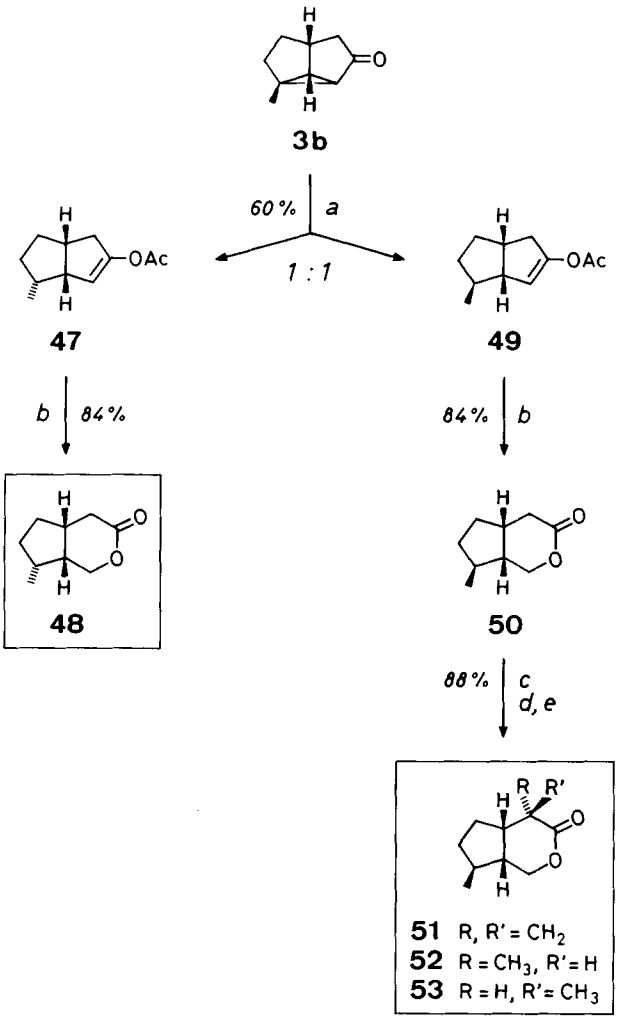


Fig. 2. Structure of bromolactone **41a** as determined by X-ray diffraction analysis [64].

After completion of the sequence **3a**→**19**→**40a**, **b**→**41a**, **b** the project failed in the last step when an exchange of the halogen of **41** for methyl proved unfeasible. Instead, the unwanted lactone **46** was formed in almost quantitative yields, evidently as a consequence of predominant proton elimination from C4 by cuprate and zincate reagents, followed by cyclization upon intramolecular displacement of the halogen at C8. The structure of **46** was elucidated by an X-ray diffraction analysis[64].

The failure to introduce a methyl group at C8 of **41** called for a change in the synthetic strategy by starting with the methylated building block (±)-**3b**. The new route included a stereo*non*selective step, a disadvantage which was compensated for by the fact that a simultaneous access to altogether four natural products was gained. Birch reduction of **3b**, followed by addition of acetic anhydride, gave a readily separable 1:1 mixture of the epimeric enol acetates **47** and **49** (Scheme 13). The two products were converted—as described above—into the lactones **48** (boschnialactone) and **50**, respectively. The latter com-

pound, after treatment with lithium diisopropylamide (LDA)/dimethyl(methylene)ammonium iodide, methyl iodide, and diazabicyclononene (DBN), furnished the first synthetic allodolicholactone **51**[65]. Following published procedures[66], **51** can be hydrogenated to iridomyrmecin **52**[65], and the latter is isomerized by base to isoiridomyrmecin **53**[67].



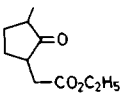
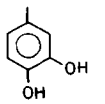
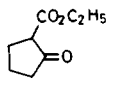
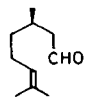
Scheme 13. Total synthesis of boschnialactone **48**, allodolicholactone **51**, iridomyrmecin **52**, and isoiridomyrmecin **53**, in racemic form, from (±)-**3b**. *a:* Na, NH_3, *t*BuOH; Ac_2O. *b:* OsO_4, $NaIO_4$; $NaBH_4$; HCl, H_2O. *c:* $CH_2{=}N(CH_3)_2I$, LDA; CH_3I; DBN, benzene (→**51**). *d:* H_2, Pd/C (→**52**) [65]. *e:* CH_3OK (→**53**) [67].

The first synthesis of allodolicholactone **51** comprised 12 steps, starting with toluene, and a total yield of 16%. The syntheses of boschnialactone **48**, iridomyrmecin **52**, and isoiridomyrmecin **53**, which like that of **51** were all achieved *via* the key compound **3b**, compare quite favorably with the most efficient of the earlier methods (Table 3).

6.2. Enantiospecific Total Synthesis of Loganin Aglucone 6-Acetate

Loganin[74] is extracted from numerous different plant species. Used in earlier times as a bitter tonic in folk medicine[73], the iridoid glucoside has up to now not found any

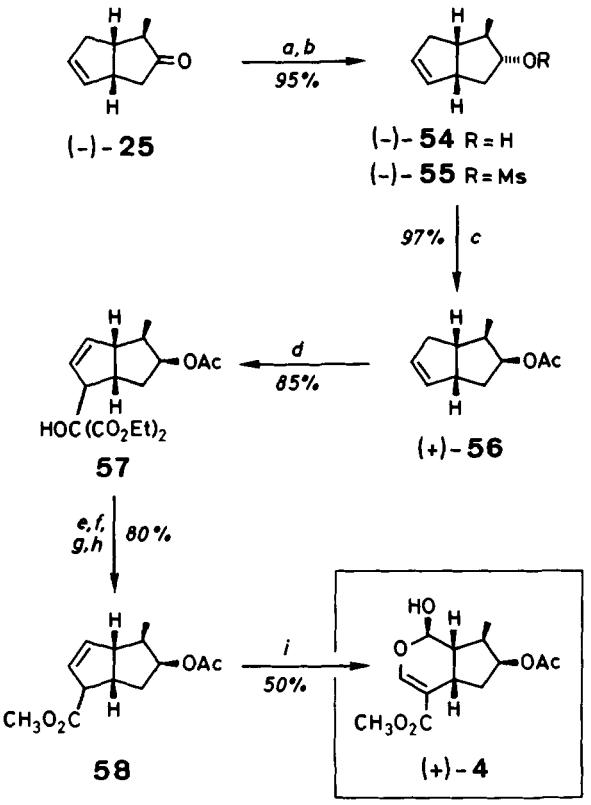
Table 3. Comparison of the new total syntheses of boschnialactone **48**, iridomyrmecin **52**, and isoiridomyrmecin **53** (cf. Scheme 13) with previous syntheses.

Product	Educt	Synthetic steps	Total Yield [%]	Ref.
(±)-**48**		9	19	This work
(±)-**48**		12	<1	[68]
(±)-**52**		13	14	This work
(−)-**52**	(+)-	11	3	[69]
(±)-**53**		14	12	This work
(±)-**53**		6	<2	[70]
(±)-**53**		10	4	[71]
(−)-**53**	(−)- 	5	<1	[72]

pharmaceutical use while other substances of this class are known[63] to exhibit interesting biological activities. With regard to biosynthesis, however, loganin plays a central role as a kay intermediate in the biosynthesis of indole and monoterpene alkaloids, and other natural products[75].

After the aglucone acetate **4** had already been transformed into loganin[73b] *via* the glucoside pentaacetate[76,77], the target of our synthesis could be confined to **4**. The access to the unsaturated ketone (−)-**25** *via* the steps (−)-**3a**→(−)-**19**→(−)-**25** (cf. Scheme 6) left in essence three more problems to be solved: the conversion of the keto group into an *exo* acetoxy group, the introduction of a methoxycarbonyl group with a concomitant allylic double bond shift, and the oxidative cleavage of the double bond to form the dialdehyde, which should cyclize spontaneously to **4** by way of the enolized β-aldehydoester group. Ample precedent for all three steps could already be found in the literature. In the synthesis of racemic loganin[77] by *Büchi et al.*, an *endo* hydroxy group was epimerized by way of an S_N2 substitution of the mesylate, furnishing the *exo* acetate. *Fleming et al.*[78] recently described a synthesis of (±)-**4** in which OsO_4 and $NaIO_4$ (in three steps) as well as ozonolysis (in two steps) were successfully tried in the cleavage of the β,γ-unsaturated ester. Finally, the ene synthesis with oxomalonate[79] proved to most

promising, in a somewhat modified version, for introduction of the ester group. *Fleming*'s loganin synthesis[78] had already applied an ene-synthetic step, resorting, however, to the detour of regiocontrolling the process by an allyl silane group.



Scheme 14. Enantiospecific total synthesis of loganin aglucone 6-acetate, (+)-**4**, from (−)-**3a** *via* (−)-**19** and (−)-**25** (cf. Scheme 6) [28]. *a:* $NaBH_4$, CH_3OH, 0 °C. *b:* CH_3SO_2Cl, $N(C_2H_5)_3$, CH_2Cl_2, 0 °C. *c:* $(C_2H_5)_4NOAc$, acetone, reflux. *d:* $OC(CO_2C_2H_5)_2$, $TiCl_4$, CH_2Cl_2, 0→25 °C. *e:* 10% KOH, room temperature. *f:* $NaIO_4$, pyridine (catalytic), room temperature. *g:* CH_2N_2, ether–CH_3OH. *h:* Ac_2O, pyridine, room temperature. *i:* OsO_4, benzene, room temperature; $Na_2S_2O_5$, C_2H_5OH, room temperature; $NaIO_4$, aqueous dioxane, 0 °C.

As was expected, the $NaBH_4$ reduction of (−)-**25** gave the *endo* alcohol (−)-**54** (Scheme 14), which was epimerized to the *exo* acetate (+)-**56** by treatment of the mesylate (−)-**55** with tetraethylammonium acetate. The subsequent ene synthesis with diethyl oxomalonate, when catalyzed with $TiCl_4$ in the temperature range from 0 to 20 °C, afforded better yields of **57** than when BF_3 or $SnCl_4$ were used[79]. The product (**57**) was sterically not uniform; this, however, is irrelevant with regard to the target structure. The degradation to the methyl ester **58** was carried out in high yield in four steps—alkaline hydrolysis, cleavage of the α-hydroxy diacid with periodate, esterification of the acid, and reacetylation of the hydroxy group. Finally, the double bond of the epimeric mixture **58** was oxidatively cleaved stepwise with OsO_4 and $NaIO_4$ to give (+)-**4**[78].

When comparing this new synthesis with previous ones (Table 4), that of *Uskoković et al.*[76] deserves special mention. Up to now, it has been the only asymmetrically induced synthesis, and is distinguished by its brevity. However, the total yield of (+)-**4** is but modest, and separation techniques are required which are hardly appropriate for larger than milligram-scale operations; this problem is not encountered in our new synthetic strategy leading to the natural aglucone enantiomer. In both *Uskoković*'s[76] and *Büchi*'s[77] syntheses the de Mayo photoannelation[81] has been chosen as the key reaction for the build-up of the skeleton of **4**. The [2+2] addition of a cyclopentene derivative to the enol of methyl diformylacetate led to the loganin framework, *via* retroaldol fission of the cyclobutane intermediate and subsequent ring closure. The two other syntheses[78,80] favored initial preparation of a bicyclopentanoid carbon skeleton, a strategy also adopted in our own work. In order to build up the second five-membered ring, the more successful of the two routes[78] employed a sequence reminiscent of method ④ (Scheme 1), *i.e.* dichloroketene addition and subsequent ring enlargement of the cyclobutanone.

Table 4. Comparison of the new total synthesis of loganin aglucone 6-acetate **4** (see Scheme 14) with previous syntheses.

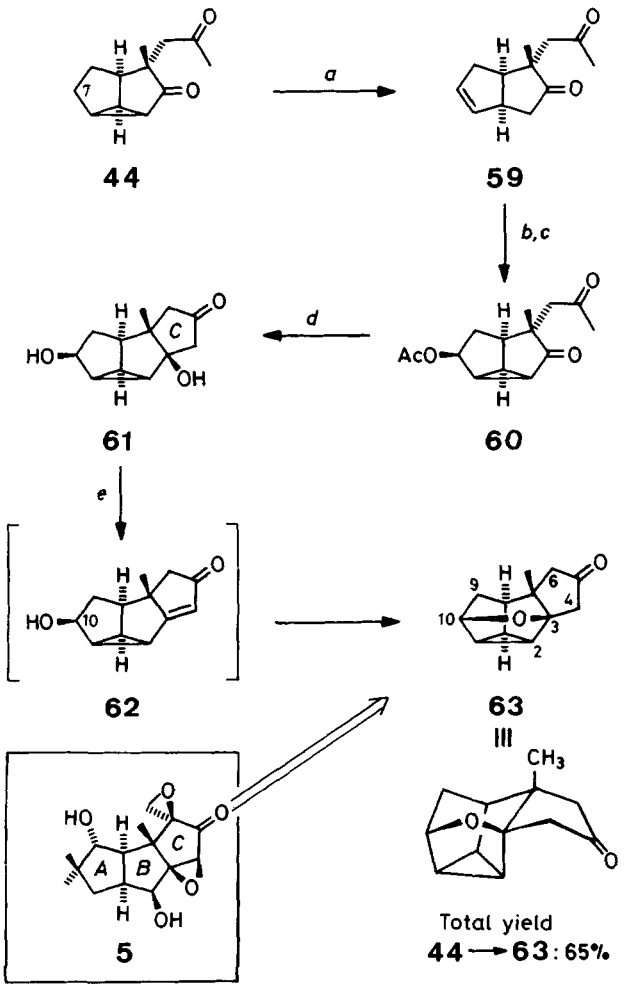
Product	Educt	Synthetic steps	Total yield [%]	Ref.
(+)-**4**		18	14	This work
(+)-**4**		6	4	[76]
(±)-**4**		13	6	[77]
(±)-**4**		14	5	[78]
(±)-**4**		15	<1	[80]

6.3. Preliminary Studies toward the Total Syntheses of Coriolin, 6a-Carbaprostacyclins, and 9,11-Dehydroestrone

6.3.1. Coriolin **5**

Products of type **61** (Scheme 15) should have a basic carbon skeleton sufficiently functionalized to serve as an attractive synthetic platform for the sesquiterpenoid coriolin **5**[82], an antibiotic with antitumor activity. For the preparation of **61**, the compound **19** was the obvious choice as a suitable intermediate. The previous studies summarized in Schemes 8 and 11 could serve as model cases for the introduction of an oxygen function at C7 and for the annelation of ring C. The actual reaction sequence comprised: Nafion TMS-induced isomerization (**44**→**59**), Prévost addition to the double bond, restitution of the three-membered ring (**59**→**60**), and cyclization by treatment of **60** for several hours with potassium *tert*-butoxide in *tert*-butyl alcohol and toluene at 80 °C.

The sequence could be carried out in an overall yield of 65% without the necessity of laborious work-up and purification procedures during the process. The primary product **61** of the ring C annelation could be intercepted when the aldol condensation of **60** was interrupted after only 5 min. The ether ring closure (**61**→**63**) could then be initiated by merely dissolving **61** together with catalytic amounts of *p*-

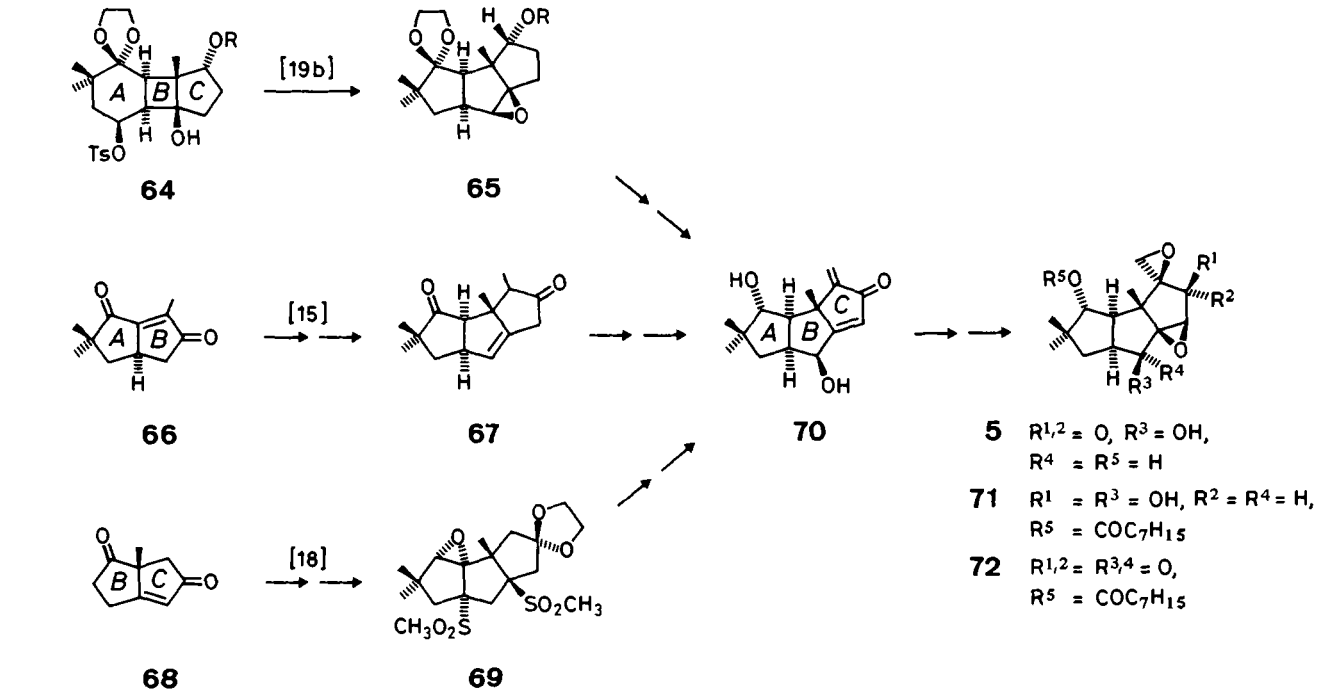


Scheme 15. First steps of an enantiospecific total synthesis of coriolin 5 from 3a *via* 19 and 44 (cf. Scheme 11). *a:* Nafion-TMS, toluene, 80 °C. *b:* AcOAg, I_2, toluene, 80 °C. *c:* DBN, toluene, room temperature. *d:* *t*BuOK, *t*BuOH, toluene, 80 °C, 5 min. *e:* as in *d*, but for 12 h, or cat. TosOH, CH_3OH, room temperature.

toluenesulfonic acid in methanol at room temperature. The α,β-unsaturated ketone **62**, presumed to be an intermediate, could not be detected. The facile cyclization is understandable upon inspection of the molecular model which shows the 10-*endo* oxygen to lie close above the enone β-carbon.

The synthesis of the diepoxyketone structure of ring C of **5** is currently in progress along routes which have been elaborated in other coriolin syntheses[15], and which take advantage of the potential $\Delta^{3,4}$-double bond and the C6 exocyclic methylene group in the α-positions to the ketone of **63**. There remain then the introduction of hydroxy groups at C2 and C9, the cyclopropane cleavage, and the *gem*-dimethylation at C10. The product **63** should possess the necessary degree of functionalization to allow selective execution of these individual steps.

Up to now, the syntheses of the racemates of coriolin **5**, coriolin B **71** and diketocoriolin B **72**, the natural enantiomers of which possess activities of pharmacological interest[82,83], have pursued the following strategies (Scheme 16). The terminal rings A and C can be joined, with concomitant formation of the centre ring B, either by a [2+2] photoaddition (→**64**)[19b] or in a metathetic sequence of thermal and photochemical steps[19d,84]. Alternatively, rings A and B can also be formed by the intramolecular addition of an aliphatic double bond to a trimethylenemethane-type diyl system contained in a starting ring C[85]. In most cases, however, the synthesis begins with bicyclic building blocks which serve as a basis for either rings A and B[15,19c,e] (*e.g.*, **66**) or rings B and C[18] (*e.g.*, **68**) (see also methods ⑨ and ⑩ in Scheme 1). The syntheses by *Tatsuta et al.*[19b] (→**64**→**65**) and *Danishefsky et al.*[15] (→**66**→**67**) converge to the intermediate **70**, which furnishes coriolin **5** on simultaneous epoxidation of both double bonds. However, the formation of the exocyclic epoxide is not stereoselective, and the yields of the last few steps range from 12[19b] to 29%[15] only. An improvement was achieved when—in



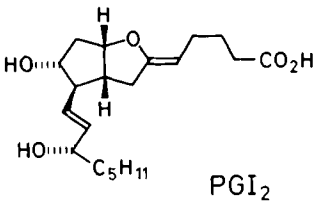
Scheme 16. Strategies of previously described syntheses of coriolin 5, coriolin B 71, and diketocoriolin B 72.

analogy to a previous synthesis of hirsutic acid[86]—first the cyclopentenone group of **70** was epoxidized stereoselectively, the keto group was reduced, and finally the exocyclic double bond was epoxidized according to the method of *Sharpless*. The overall yield of **5** after 24 steps was only 0.2%. The synthesis of **71** together with a previously described conversion of **71** into **72**[82b,87] also constitutes a formal total synthesis of the diketone.

Several other syntheses have been reported, all of which lead to the intermediate **70**[18,19c-e]. Among these, the work by *Trost et al.*[18] deserves special mention since it has been the only one so far exploring an enantioselective access to **70**, by way of **68** (e.e. 40%) and **69**[114]. The use of **44** (Scheme 15) promises to be the first satisfactory solution to the problem of enantiomeric resolution (with an enantiomeric excess of >98%), hopefully coupled with a practicable yield of the final product.

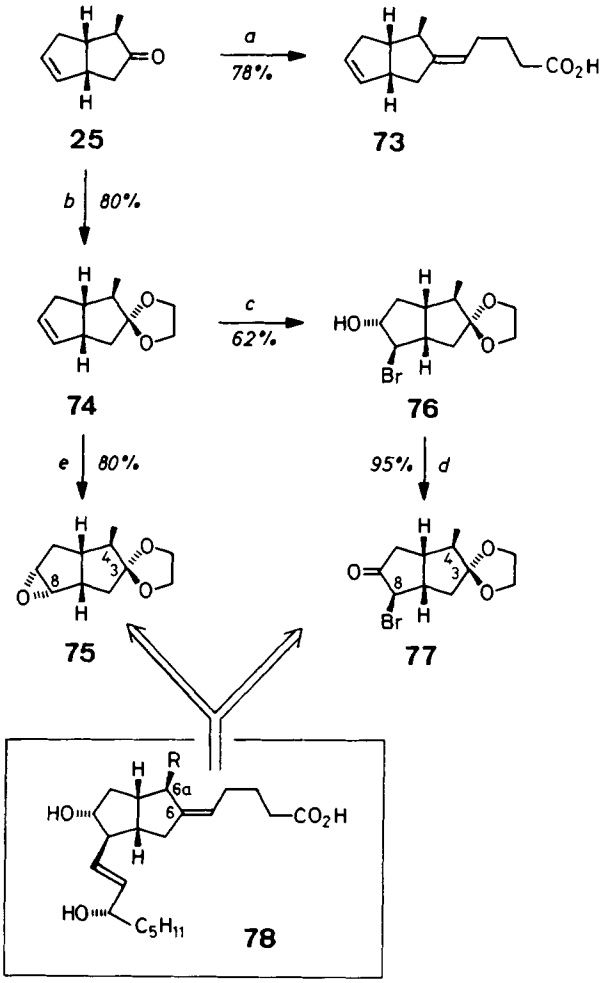
6.3.2. 6a-Carbaprostacyclins **78**

6a-Carbaprostacyclin **78** (R=H; other names: carba-PGI_2, carbacyclin, 9(O)-methanoprostacyclin) promises to eventually serve as a blood anticoagulant[88] in therapeutical applications as widely as do some naturally occurring prostaglandins[89]. Compound **78** (R=H) is the carbocyclic analogue of prostacyclin (=PGI_2)[90], the representative of greatest pharmacological importance among the prostaglandins. Such bicyclopentanoid analogues are more resistant to hydrolysis[91] than PGI_2, which is an essential advantage in therapy. This distinction has made the carbaprostacyclins a target of concerted synthetic efforts in the past few years[5,92-95].



PGI_2

Two combinations of functional groups, which are readily available *via* the unsaturated ketones **19** and **25** (Scheme 6), can now be envisaged to provide an improved synthetic access to 6a-carbaprostacyclin **78** (R=H) as well as—for the first time—to 6a-*exo*-alkylated derivatives (*e.g.*, **78**, R=CH_3): the ketone acetals with an *endo* epoxide such as **36b** (Scheme 8) and **75** (Scheme 17), and those with an α-bromoketone group such as **77**. The latter two intermediates were prepared as follows: On the one hand, oxidation of the unsaturated acetal **74** with *m*-chloroperbenzoic acid gave a 9:1 mixture of stereoisomeric epoxides (>95% yield). The major component **75**, with *endo* configuration, could be isolated by chromatography on a Florisil column (80% yield). On the other hand, treatment with *N*-bromosuccinimide in aqueous tetrahydrofuran converted **74** into a mixture of bromohydrins, from which the isomer **76** was separated by chromatography on silica gel. Although inferior to the highly selective step **74**→**75**, the yield of 62% **76** is sufficient to render this latter variant an alternative synthetic route worth further exploration. Similar transformations of the corresponding lactonic precursor of PGI_2 had proved non-selective[96]. The pure bromoketone **77** was obtained without further purification upon oxidation with *N*-chlorosuccinimide (NCS)/dimethyl sulfide[97].



Scheme 17. First steps of the enantiospecific total synthesis of a 6a-carbaprostacyclin **78** (R=CH_3) from **3a** *via* **19** and **25** (cf. Scheme 6). *a:* $Br(CH_2)_4CO_2H$, $(C_6H_5)_3P$, *n*BuLi, THF, room temperature. *b:* $HC(OCH_3)_3$, $(CH_2OH)_2$, TosOH. *c:* NBS, THF, H_2O, 0 °C. *d:* NCS, $(CH_3)_2S$, $(C_2H_5)_3N$, toluene, −30 °C. *e: m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 0 °C.

The remaining tasks of the planned synthesis are restricted to the introduction of the side chains at C3 and C8 of **75** and **77**. For both, elaborate procedures are found in the literature. The δ-side chain is normally attached to C3 in a Wittig reaction, affording a mixture of isomers which differ with regard to the configuration of the double bond[5,93,94]. Since only the *E* isomer in formula **78** (R=H) exhibits the desired biological activity[5,94], we first began a synthesis of the as yet unknown methyl homologue **78** (R=CH_3). It was expected that the *exo* methyl group at C4 would direct the Wittig condensation with the adjacent keto group, still protected as the acetals in **75** and **77**, to selectively furnish the required configuration. And indeed, in an exploratory experiment with **25** exclusively the product **73**, with the correctly configurated double bond, was formed in high yield. The remarkably high degree of orienting influence on the Wittig reaction had not been exploited in previous work[5,93-95]. A likely obstacle was the

difficulty in carrying out stereoselective methylations on the bicyclo[3.3.0]octane systems used in these syntheses.

In the synthesis of PGI_2, *Corey et al.*[98] employed the Gilman reagent, lithium bisvinyl cuprate, to attach a ω-side chain precursor at C8 by opening of the *endo* epoxide with a high degree of the desired regioselectivity. The final build-up of the ω-chain was thus completed in three further steps. The same method should also be applicable to **36b** and **75**. A direct introduction of the entire ω-chain using a mixed cuprate reagent[99] which already contains the intact side chain, has been achieved so far only with 2,3-*endo*-oxidobicyclo[3.2.0]heptan-6-one acetal[96]. Although modest, the regioselectivity was still practicable. It is now of particular interest to note that in this special case the same combination of functional groups, epoxide and acetal was encountered as would be in **36b** and **75**. Moreover, the spatial arrangements are quite similar. The procedure may therefore be applicable to our intermediates as well. The overall synthetic enterprise may prove more simple in this case than the route involving the Gilman reagent.

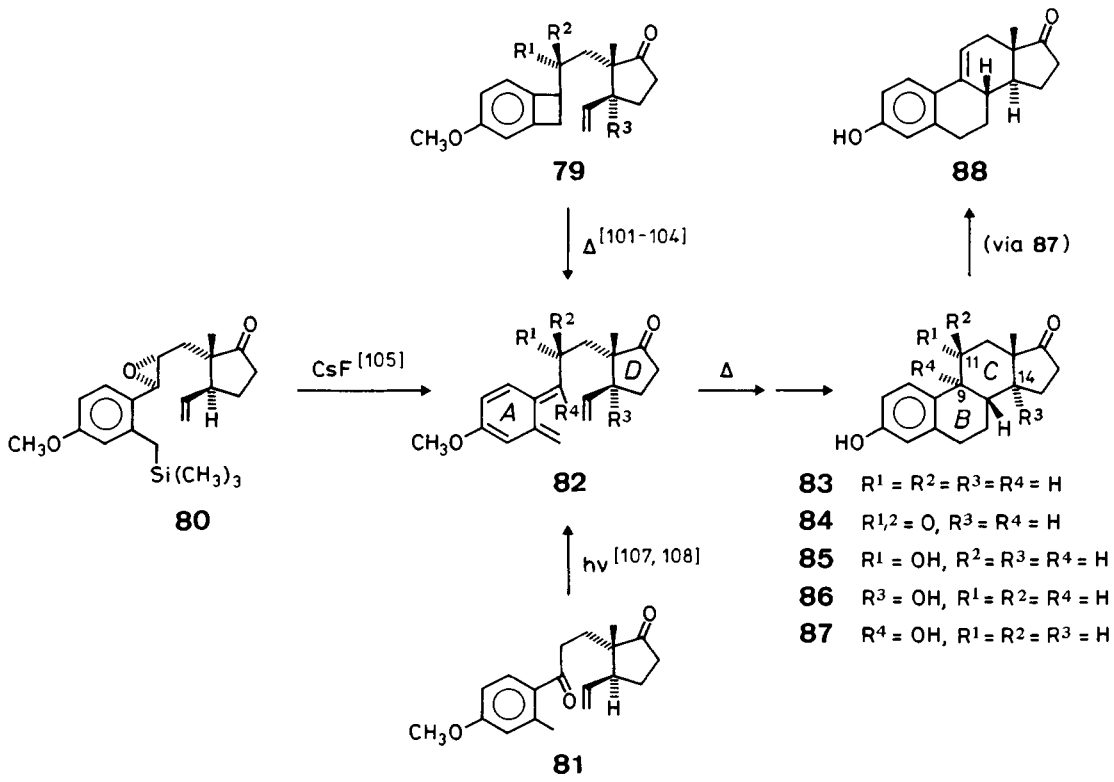
A possible alternative for the build-up of the ω-side chain begins with an alkylation step[5,93,95]. From among our set of intermediates, the bromoketone **77** should be an appropriate precursor.

Thus we are encouraginged to predict that the intermediates **36b**, **75**, and **77** will open up the hitherto most productive synthetic access to 6a-carbaprostacyclins **78** (R = H, alkyl) and 4,4-dialkyl derivatives, providing end products of high enantiomeric purity. For example, starting from benzene and using the mixed cuprate reagent, one may anticipate a total synthesis of **78** (R = H) in 12 steps, and of **78** (R = alkyl) in 13 steps. Employment of the bisvinylic cuprate would increase the sequences to 16 and 17 steps, respectively. In comparison with this prediction, the only completed synthesis of optically active **78** (R = H)[94] appears much less advantageous. It began with relatively expensive, optically active intermediates and led, *e.g.* starting from the Corey lactone[100], to a *E,Z*-mixture of **78** (R = H) in 17 more steps.

6.3.3. 9,11-Dehydroestrone **88**

Numerous novel and imaginative total syntheses of steroids have been developed in recent years mostly with the female sexual hormones estrone and estradiol as the target molecules. Both are widely used to regulate ovulation. The most pressing need at present is the development of more economic syntheses of optically active structural modifications of the estrogens in the hope of discovering analogues with fewer side effects on long-term application.

Most of the new syntheses use a building-up scheme in which the terminal rings A and D are linked first, and then the central rings B and C are simultaneously formed in a cyclization reaction: A + D → AD → ABCD (Scheme 18). This basic procedure has also been used for the generation of estrogens containing a functionalized ring C. The second step was accomplished either using purely thermal[101-105] or combined photochemical and thermal reaction sequences[107,108]. The double ring closure always proceeds *via* a regio- and stereoselectively well-controlled internal [2 + 4] cycloaddition of an *o*-quinodimethane-type precursor **82** which is generated *in situ*. This key intermediate can be generated by thermal isomerization of the appropriate benzocyclobutene **79**[101-104]. In two cases, the method led to oxygenated estrone derivatives: *Oppolzer*[101] prepared



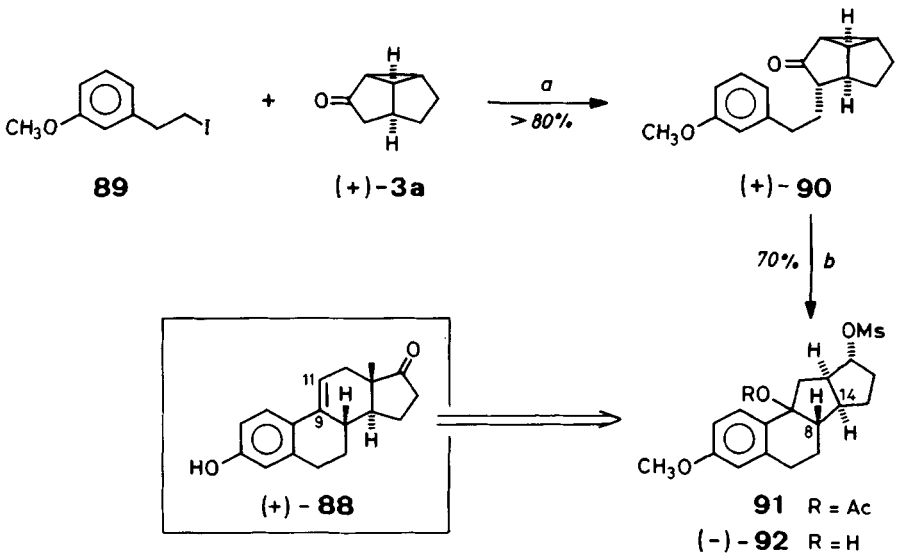
Scheme 18. Key steps of previously described enantiospecific total syntheses of estrone **83**, 11-oxoestrone **84**, 11α- **85**, 14α- **86**, 9α-hydroxyestrone **87**, and 9,11-dehydroestrone **88**.

the natural enantiomer of 11-oxoestrone **84**. The resolution of the racemate was carried out at the stage of the monocyclic (ring D) precursor of **79** (R^1, $R^2=O$, $R^3=H$). *Kametani et al.*[104] started from a 1,3-oxygenated ring D precursor (→ **79**, $R^1=R^2=H$, $R^3=OH$) in order to obtain the racemic form of a 14-hydroxy steroid **86**. In a synthesis aimed at racemic 11α-hydroxyestrone **85**, the *in situ* generation of an *o*-quinodimethane intermediate was achieved even at room temperature, when compound **80** was treated with cesium fluoride (→ **82**, $R^1=O^{\ominus}$, $R^2=R^3=R^4=H$)[105].

The photochemical variant consists of an intramolecular hydrogen abstraction by the optically active aromatic ketone **81** (Norrish type II photoreaction), leading to the *o*-quinodimethane **82** ($R^1=R^2=R^3=H$, $R^4=OH$). In this way, *Quinkert et al.*[107,108] opened up a novel access to 9α-hydroxyestrone **87**, 9,11-dehydroestrone **88**, and estrone **83**. For the synthesis of the oxygenated and unsaturated estrones 10 steps (formation of the racemates)[105] or 15 steps (formation of pure enantiomers)[101] are necessary if in each case the appropriate monocyclic ring D precursor is considered as starting material. With one exception only[108], these are rather costly cyclopentenone derivatives[101,104,105]. With regard to the number of steps—but not the overall yield—the earlier syntheses of 9,11-dehydroestrone **88** reported by *Crispin* and *Whitehurst*[106] and by *Cohen et al.*[109] still appear quite attractive, particularly in view of the fact that the starting material, an indane derivative of the Wieland-Miescher type, has become readily available in optically active form[110]. *Posner et al.*[111], in a more recent synthesis of **88**, underscored all previous efforts with respect to the number of reaction steps using a one-pot procedure which affords the end product in 5.5% yield starting from 6-methoxy-1-tetralone in an AB+D→ABD→ABCD sequence. The major drawback is that the method has so far been restricted to the synthesis of racemic material.

Our own work[112] assumes a route of the type A+CD→ACD→ABCD and it is founded on the prospect that, starting with an alkylation of (+)-**3a**, relatively few steps should lead to optically active 9,11-dehydroestrone **88** (Scheme 19). Treatment of the lithium enolate of (+)-**3a** with the phenylethyl iodide **89** at −20 °C smoothly furnished the *exo*-alkylated product (+)-**90**. Substituting bromide or tosyloxy derivatives for the iodide **89**, and sodium or potassium for lithium as the enolate counterion reduced the yields substantially, in accord with earlier experience[108,113]. The cyclization of (+)-**90** could be accomplished by treatment with acetyl methanesulfonate. The resulting tetracyclic acetoxymesylate **91** was hydrolyzed during the work-up to form the crystalline hydroxymesylate (−)-**92**. The mechanism of the ring closure is not yet clear. Undoubtedly the nucleophilic mesyloxy group was incorporated in the primary step of the cyclopropane cleavage[53,57], and the enol acetate (cf. **20**, Scheme 6) should have been formed at the same time. The subsequent closure of ring B corresponds to an acid-catalyzed cyclization, possibly a consequence of the difficulty to prepare the reagent without any contamination with acid.

Starting from benzene, the overall yield of optically active compound **92** (enantiomeric excess >98%) was 10%, with the last two (**3a**→**90**→→**92**) of altogether 8 steps not having yet been optimized. The only two asymmetric carbon atoms of synthetic importance, C8 and C14, were formed and retained, respectively, in the highly selective *exo* alkylation of (+)-**3a**. On continuing this project, attention will be focussed on the ring C enlargement, the introduction of the angular methyl group, and the epimerization of the secondary hydroxy function—reactions with ample precedent in steroid chemistry. This outlook hopefully justifies our optimism that the photoproduct **3a** in an application beyond the domain of polycyclopentanoid compounds, may open up a novel and economic route to optically active steroids possessing a functionalized ring C.



Scheme 19. First steps of an enantiospecific total synthesis of 9,11-dehydroestrone **88** from 3-methoxyphenylethyl iodide and (+)-**3a**. *a*: LDA, dimethoxyethane, −20 °C. *b*: $CH_3SO_3COCH_3$, $CHCl_3$, room temperature; yield of both steps not yet optimized.

7. Conclusions and Outlook

We have presented a synthetic concept with a photochemical key step which is particularly attractive with regard to its unusually wide versatility, and to the extraordinarily clean and selective reaction courses. Irradiation conditions have been used throughout which should pose no serious problems to scaling-up.

The parent building block, tricyclo[3.3.0.$0^{2,8}$]octan-3-one **3a**, is readily accessible from commercially available chemicals. Its resolution into both enantiomeric forms is quite simple, and it is amenable to a large variety of transformations. Compound **3a** is thus qualified as one of the most attractive starting materials for the total synthesis of optically active cyclopentanoid substances. Only the building blocks with a higher degree of substitution (**3b**, **c** and **9d**, **e**), although also readily accessible in their racemic forms, require further improvements of the optical resolution methods in view of their most promising potential as intermediates *en route* to non-linearly fused polycyclopentanoid natural products, such as isocomene (from **3c**) and the pentalenolactones (from **9e**).

In addition to the synthetic projects which have been taken up so far, one may consider probing into modifications of the basic concept in various ways, such as the following: Incorporation of heteroatoms may lead to, *e.g.*, alkaloid structures. Cleavage of the central 1,5-bond of **3** could open a route to medium-sized rings, with the ultimate goal of synthesizing sesterpenes such as the ophiobolins. Furthermore, a stereocontrolled access to acyclic elements appears feasible by way of oxidative bond fissions, and thus bring classes of macrolides and polyether ionophores within synthetic reach.

We have summarized the synthetic work of many notable young collaborators, Dr. A. Cánovas, Dr. C. Carter, Dr. S. Chandrasekhar, Mr. G. Mikhail, Mr. P. Ritterskamp, Dr. K. Nakano, Dr. U. Pati, Dr. P. R. Raghavan, Dr. K. Tsutsumi, and Mr. B. Wietfeld, supported by the able technical assistance of Mrs. H. Adams-Schulze. The results of their enthusiastic and intense collaboration have not yet been published in any detail, if at all. The authors of this account should therefore like to gratefully acknowledge for the first time the relentless efforts and contributions of the whole group.

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Immobilized Biomaterials—Techniques and Applications

By Bhavender P. Sharma*, Lorraine F. Bailey, and Ralph A. Messing

The immobilization of enzymes, cofactors and whole cells offers the potential of economical exploitation of biomaterial activity. Enzymes or cells can be immobilized by binding to carriers through adsorption or covalent linkages or by entrapment in a polymer matrix or microencapsulation. The development of immobilized biomaterial systems requires the involvement of biochemical, kinetics and reactor design principles. Examples of commercial scale applications of immobilized biomaterial systems are the production of a fructose-rich syrup from starch and the synthesis of L-amino acids by selective hydrolysis of *N*-acyl-D,L-amino acids.

1. Introduction

The standard of living that the high-technology industrial nations have achieved during the first three-quarters of the twentieth century has led to increased demands for raw materials, energy, and, last but not least, food. In addition, the increased rate of industrial mechanization and activity has led to numerous ecological problems, which, in turn, appear to forecast diminishing supplies of raw materials.

The intent of this introduction is not a prediction of "gloom and doom" but rather to demonstrate the need of alternatives for conservation and of less wasteful approaches for the utilization of our natural resources. The immobilization of biomaterials is a useful technology for attaining these objectives. An overview of the techniques and applications in the immobilized biomaterials field is presented in this paper.

Modern man has ravaged the bowels of the earth for minerals; over-abundantly harvested vegetation; and wantonly spewed waste into the streams, water bodies, atmosphere, and upon the surface of the solid earth. These wastes have, in turn, putrified his environment. With this putrifaction he has destroyed much of his animal and plant resources.

Increased costs due to the diminishing supply of certain materials such as aluminum, copper, chromium, *etc.* have persuaded our society to initiate a recycling program. The light dawns!

Putrifaction pollution, however, does not arise from inorganic materials but rather from organic molecules that are subject to microbial attack. These waste organic molecules represent an additional rich source of raw materials. If this waste were to be harvested, the following items could be produced by a recycling process:

1) fuel in the form of methane or alcohol,
2) glucose, the major nutrient for the production by fermentation of antibiotics and other industrial commodities,
3) synthetic petroleum stocks for plastic production,
4) food and food supplements for livestock,
5) vitamins and hormones.

It is clearly apparent that waste will not exist if proper utilization of this squandered resource is adequately planned.

Plants, animals, and microbes are harvested for the production of biological catalysts, enzymes, which in turn are employed in processing foods and pharmaceuticals. Since these biological catalysts are soluble and generally employed in batch reactions they are used but once, and either they are destroyed in further processing, or they cannot be recovered from the reaction economically. An enzyme is a precious material harvested, sometimes, at the sacrifice of a precious life. Immobilization technology offers the opportunity to reuse the biological catalyst and thus reduce the consumption of life and the need for additional resources to produce that life.

The needs for the immediate future will probably be supplemented with methane or natural gas produced by immobilized cells. Although this gas is relatively clean, the preferred fuel which causes no atmospheric pollution is hydrogen. A hydrogen fuel economy, however, is at least fifteen years hence. Our society is neither geared to employ hydrogen nor prepared to transport this fuel over great distances in large quantities. The hydrogen economy of the future may well be supplied from solid-phase reactors which are capable of either splitting water to produce hydrogen and oxygen (biophotolysis) or stripping hydrogen from photosynthetically produced, organic molecules.

2. Immobilization[*]

The knowledge base accumulated on enzyme immobilization studies has grown to very large proportions and this wealth of information is one of the primary reasons for the advance in enzyme engineering that is being witnessed currently. The slower-than-predicted introduction of immobilized enzyme systems into commercial use has been the result of numerous factors. Some of these factors have been the development of more practical techniques of immobilization, frequently with nontoxic chemicals, the long term experiments required for approval of the total biological composite for use in food applications, learning to control microbial contamination in biological reactor systems, and

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[*] For detailed reviews see *e.g.* [1-6].

enzymes possessing characteristics limiting their economic success, to name a few. The engineering of enzymes with more useful characteristics will overcome some problems encountered that have prevented commercial processes from developing.

2.1. Advantages to Immobilization

Besides reuse of biological catalysts and therefore reduced consumption, immobilization can offer numerous advantages in the operational handling of these materials. It can be employed to stabilize an otherwise labile substance by covalent multi-point attachment or by confinement in a stabilizing and protecting environment (Fig. 1)[7,8].

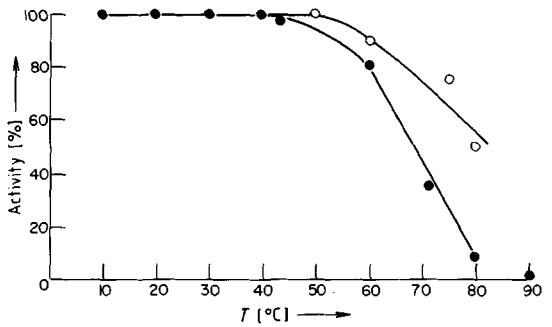

Fig. 1. Example of the increase in thermal stability of an enzyme by immobilization. This figure is a comparison of papain in soluble form (● — ●) and immobilized on porous glass (○ — ○) on storage at increasing temperatures for 30-minute periods. The activity remaining was measured at 25 °C (after [8]).

In so doing, chemical and physical properties can be selectively altered to one's choice of application. Not only are batch reactions possible, but continuous processes can be considered. Multiple enzyme immobilization can confer greater efficiency in consecutive multi-step reactions. Rate enhancement results because of an abnormally high local concentration of intermediates (the products of one enzyme which become substrates for the next one) relative to the conditions existing in a free solution. Multiple enzymes also mimic the cell environment where complex enzyme systems are common.

2.2. Immobilization of Microorganisms or Enzymes?

Many extracellular microbial enzymes are produced in large enough quantities to be used in industrial processes; however, the cost of isolating and purifying intracellular enzymes for commercial processes can dampen the profitability sufficiently for their use to become unattractive. Nonetheless, there are advantages to the isolated enzymes that must be balanced against cost based upon the nature of the conversion process. Isolated enzymes offer greater purity and the possibility of apparent modified kinetics which, in turn, may yield higher conversion of products less contaminated by miscellaneous materials. Immobilizing microorganisms containing the catalyst of interest combine the advantages inherent in the use of immobilized enzymes with those of microbial fermentation processes.

Immobilizing the whole cell should be considered when the extracted enzyme is unstable, since retaining the enzyme within its natural surroundings preserves its stability. Additional considerations for cell immobilization are: that no enzyme-catalyzing interfering side reactions be present within the cells (although often these can be deliberately inactivated); that the cells retain greater enzyme activity than is possible with immobilized enzymes; that the reactor volume per unit of product is much smaller for the continuous, immobilized cells method than for the conventional fermentation process. A conceivable short-coming could be encountered by substrate and product transport resistance of cell wall and cell membrane.

2.3. Effects of Immobilization

Upon immobilization, alterations in the properties of enzymes occur which result from cumulative reactions. An immobilized preparation placed into a solution of substrate, activators or other components at a given pH and ionic strength, does not assure that the conditions in the medium immediately surrounding the enzyme will be identical to those in the external bulk solution[9]. This phenomenon, referred to as the microenvironmental effect, can be the result of charges or physicochemical properties of the supporting matrix[8] or may be caused by diffusional limitations (Figures 2 and 3).

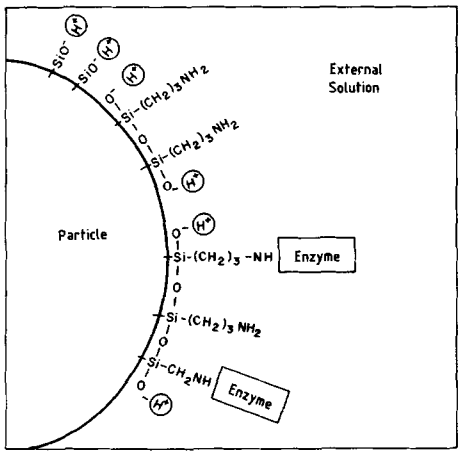

Fig. 2. Effect of pH upon the microenvironment of an immobilized enzyme on porous glass with primary amino groups (schematic). An accumulation of H^+ ions at the surface creates a more acidic environment than that of the external bulk solution (after [9]).

Kinetic constants and other enzyme parameters investigated on immobilized preparations are not true values equivalent to homogeneous reactions because of these factors, and measured values are referred to as apparent specific activity. Operational activity should be obtained under the specific process conditions under study.

In making a selection for a method and materials for immobilization of a whole cell, the choice must be dictated by the ultimate use of the cell and the effect of the immobilization procedure on the integrity of the cell. Whether or

not the enzyme of interest within a cell retains its activity only in viable cells, or only in intact cells, or is stable in non-growing cells will narrow the types of methods that

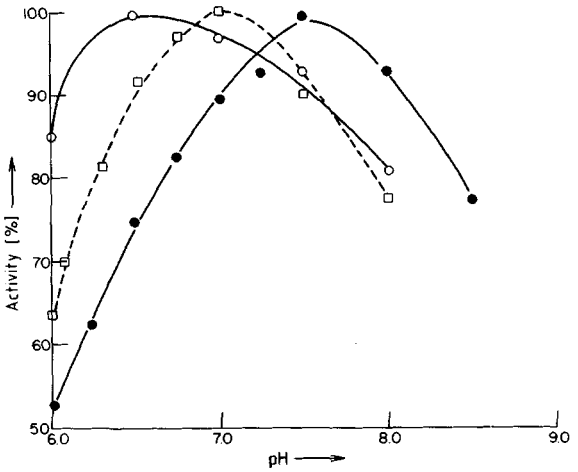

Fig. 3. The effect of increasing pH on the activity of soluble papain (O—O) and two papain immobilized samples on derivatized porous glass using heat-denatured casein as substrate. The carrier charge changed the profile as well as immobilization. □---□, negatively charged surface; ●—● positively charged surface (after [8]).

can be employed. In such cases as for the regeneration of cofactors, the system will be useful only as long as the cells are viable, thereby determining the life of the system. Under certain conditions, it may be necessary to supply a nutrient to retain the integrity and growth of the cell.

2.4. Methods of Immobilization

Briefly, enzymes or cells can be immobilized by binding to carriers through adsorption or covalent linkages or by entrapment within a matrix or microcapsule (Fig. 4).

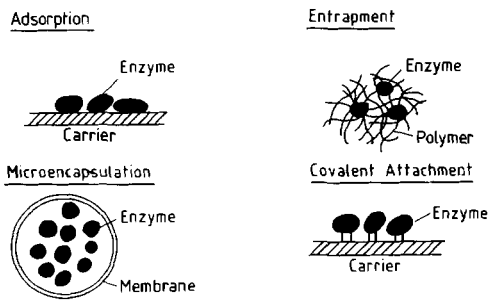

Fig. 4. Schematic representation of the general immobilization techniques.

Frequently, immobilization of a protein cannot be attributed to purely chemical or physical means, and quite often successful immobilization is dependent on both. The choice of carrier and the method of immobilization are nearly inseparable and dependent upon numerous factors which will be further elaborated as the discussion progresses.

2.4.1. Adsorption

Adsorption is the attachment of a protein to the carrier surface which has not been specifically functionalized for covalent bonding. The mechanism of adhesion may include simple ion-ion interactions, hydrogen bonding, hydrophobic interactions, or covalent bonding. The stability of the adsorbed protein will depend upon the additive strength of those bonds formed under the conditions of immobilization and those bonds maintained under the application conditions that are finally employed for the immobilized preparation. In theory, adsorption should be a reversible process; but in practice, it may or may not be. The degree of adsorption or desorption will be contingent upon a balance of parameters including pH and ionic strength of the medium, presence of substrate, protein concentration, time and temperature, as well as inherent characteristics of the enzyme and the support. The reversibility of adsorption may be of practical advantage, since intact recovery of both the enzyme and the carrier may be possible.

Operationally, adsorption is probably the simplest and most economical of the immobilization methods.

2.4.2. Covalent Attachment

Covalent bonding can involve the activation of the support material for reaction with protein groups, or the use of a coupling reagent for linkage of the protein and support matrix, or the activation of the protein for binding to the support. It is by far the most intensively studied of the immobilization techniques (Fig. 5). The overall configuration of a protein is designed to bring the residues of the active site into a precise arrangement of charge and microenvironment. Therefore, in the process of immobilization, care must be exercised to retain that active conformation. Failure to achieve an active, immobilized preparation may often be due to inactivation of the enzyme. If necessary, the active site can be protected by the presence of substrate or a competitive inhibitor during coupling. These protective molecules can be removed afterwards. For the most part, the chances of binding at the active site are slight, since the area of the active site is quite small in comparison to the overall area of the protein. Further, the active site is frequently located in a recessed portion with entrance dependent upon size, charge characteristics, and stereochemistry of the coupling agent. Sometimes, an increase in activity is observed after initial operation due to additional enzyme active sites opening up in the presence of substrate which may formerly have been bound to the carrier or adjoining protein molecule.

The amino acid groups suitable for binding are based upon their reactivity, their concentration within the protein, their location, and the microenvironment in which they are placed. The amino groups have been extensively used as sites for covalent binding, as they readily react with aldehydes, diazonium salts, isocyanates, acylating and alkylating agents.

Covalent attachment is considered the most permanent of the immobilization methods.

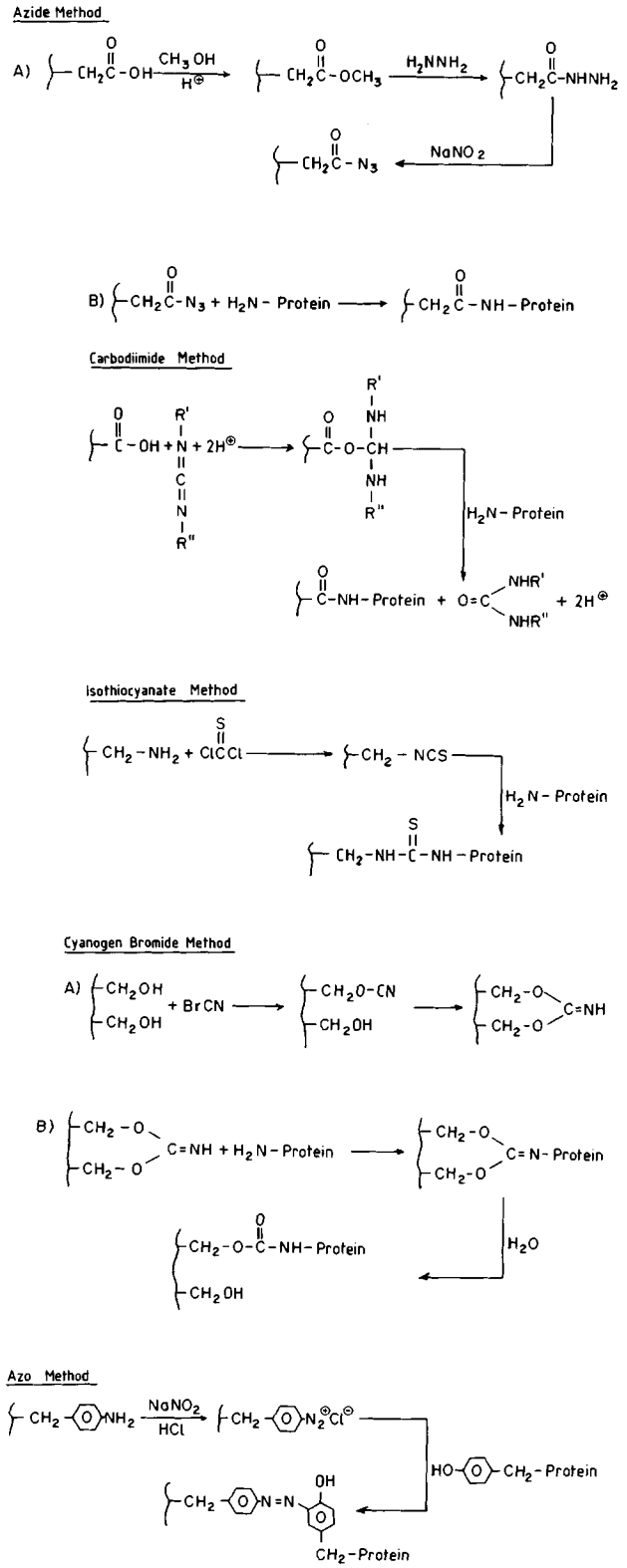

Fig. 5. Methods most commonly used for the immobilization of enzymes by covalent bonding.

2.4.3. Matrix Entrapment

To entrap an enzyme, either a cross-linked polymeric network is formed around the enzyme molecule, or the enzyme is placed inside a polymeric material, and the polymeric chains are then cross-linked. This is usually followed by disruption of the polymeric mass into the desired particle size. The most commonly used polymeric material is the polyacrylamide gel system; although silica gel, starch, and silicone rubber have also been employed for this technique. Entrapment is probably the most popular method of immobilization of microbial cells, although other methods have been successfully utilized. In recent years, materials like alginic acid and carrageenan have been employed which form beads of gel when the cell-containing solution of these materials is extruded into salt solutions such as $CaCl_2$. The advantage of this type of material is its nontoxicity to the cells—enzymes, also, are amiable to entrapment with these materials.

The end result is the confinement of the enzyme or cells within lattices of gels which permits the free diffusion of appropriate sized substrate and product molecules. These molecules are limited to low molecular weight due to the pore size requirement needed to prevent escape of the high molecular weight enzyme. The problem of enzyme release is always present because of the unequal pore distribution of the gels; however, it is possible to overcome this by cross-linking the entrapped enzyme with a bifunctional reagent such as glutaraldehyde.

The solubility of the enzyme within the entrapment medium may limit the maximum loading of the enzyme. The actual specific activity of the entrapped enzyme may be determined by such factors as microenvironmental effects of localized pH or ionic strength and unequal partitioning of the substrate, or inhibitors of the enzyme activity. In theory, this method of immobilization does not involve a disruption of the enzyme configuration.

2.4.4. Microencapsulation

Microencapsulation is only applicable to enzymes whose substrates and products are of rather low molecular weight. There are two methods of forming membrane microcapsules, one based upon coacervation (a physical phenomenon) and the other upon interfacial polymerization (a chemical process). The thickness and permeability of the membrane is influenced by the organic solvent composition, the concentrations and chemical components utilized to form the membrane, as well as the time of capsule formation. In principal, no chemical modification of the enzyme occurs, and thus, there should be no changes in the inherent properties of the enzyme. However, diffusional effects and enzymatically generated microenvironments can bring about apparent alterations in enzyme properties.

While this immobilization method is directed more toward medical use, there may be circumstances where the membrane protection would be beneficial and applicable to industrial processes.

2.5. Carrier Selection

The components comprising an immobilized enzyme system are the enzyme, the carrier, and the method of attachment. Other contributors such as pH, ionic strength, pressure, agitation, cofactor delivery, substrate delivery,

and product removal may affect the performance of the immobilized enzyme. The final system should be evaluated by the sum of the cost of the contributions of the individual components *versus* the performance value of the system. In making a carrier selection, the carrier properties of morphology, surface contributions, composition (see Table 1), and regeneration should be assessed. All should contribute synergistically to the enzyme activity in the application environment for optimum economic performance.

Table 1. Carriers for biomaterials (selection).

Controlled pore glass and ceramics (alumina, silica, titania)
Polystyrene
Ion-exchange resins
Agarose and Sephadex
Nylon
Collagen
Polysaccharide supports (cellulose, dextrose, starch, agar)
Acrylic copolymers
Silicone rubber
Silica gel
Bentonite
Clay
Magnetic supports

The morphology of the carrier is extremely important with respect to surface area and pore parameters. Superimposed upon this is the gross configuration of shape in a particulate, spherical, sheet, tube, fiber, or membrane form. Since the enzyme is attached to the surface, the surface area and thus the loading of the enzyme are greatly affected by whether or not the carrier is porous[3, 10]. Nonporous supports are very low in surface area; however, because of this characteristic diffusional constraints are minimal since the protein is located only on the external surface. While porous supports have much larger surface areas, much of the surface is internal; nevertheless, the potential for maximizing activity is greatly enhanced by this feature. In addition, the internal surface offers a protection from the turbulent and sometimes harsh, external environment as well as microbial attack. A variety of controlled pore (narrow pore distribution) and broad pore carriers are now available. These can be used to optimize biomaterial activity (Fig. 6—8).

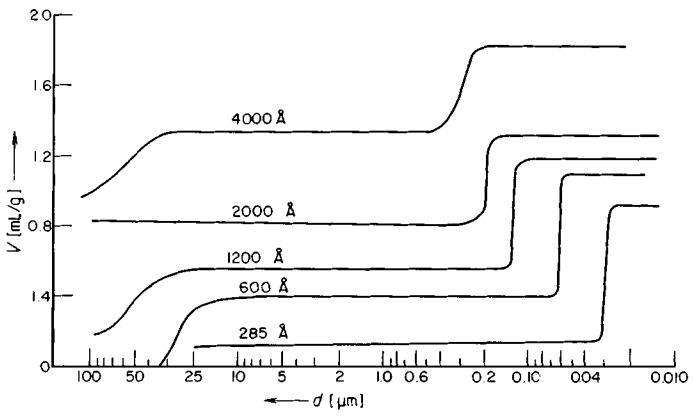

Fig. 6. Relationship between pore diameter d and pore volume V in glasses with controlled pore size. The midpoint of the vertical section in each curve represents the average pore diameter. The steeper the slope of the vertical section, the tighter is the pore control (after [10a]).

Also to be considered in carrier choice are the intrinsic features of whether the material is inorganic or organic. Inorganic carriers offer rigidity and lack of deformation. They can be expected to undergo abrasion in continuous stirred reactors but handle well in plug-flow reactors, and large pressure drops are not encountered. Organic carriers, on the other hand, are more flexible and elastic, which promotes the ease in which a variety of configurations can be produced, *e.g.*, a thin membrane. They resist abrasion

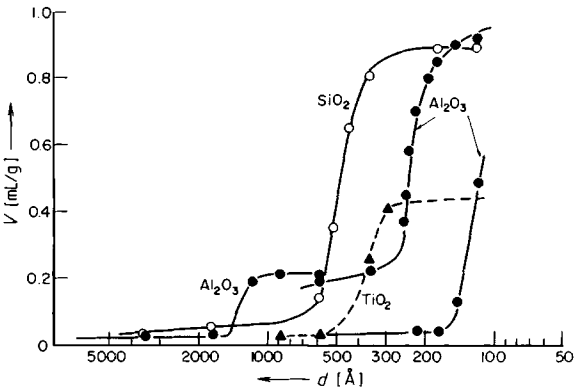

Fig. 7. Relationship between pore diameter d and pore volume V in controlled-pore ceramics as determined by mercury intrusion (after [10b]).

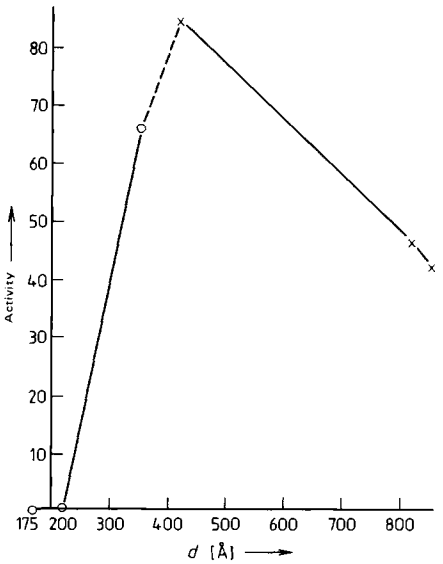

Fig. 8. Activity of glucose oxidase (in units/g) as a function of pore diameter d, cumulative data (after [7]).

in continuous-stirred reactors, but greater pressure drops will be experienced with their use in plug-flow reactors.

The ability to regenerate the immobilized enzyme system significantly effects its economics. The three approaches to regeneration are: 1) the reactivation of the immobilized preparation by removal through appropriate washing of the material plugging the pores that produced inactivation; 2) regeneration of the immobilized preparation by adding fresh enzyme to the system; and 3) regeneration of the carrier by removing old enzyme by chemical or physical means and initiating immobilization procedure anew.

3. Technical Application of Immobilized Biomaterials

3.1. Introduction[*]

Suppose the above-mentioned advantages in using immobilized biomaterials appear promising for a specific problem, the next step is the development of a suitable system. It is likely to be carried out in the context of questions relating to the selection of a carrier, the immobilization technique, and the reactor system. Ideally, these three facets should be considered simultaneously. This section will deal with the application of some concepts in developing an immobilized biomaterial system—the kinetic and mass transfer aspects, and the criteria and strategy in selecting, developing and operating a reactor system.

3.2. Kinetics of Reactions Catalyzed by Immobilized Biomaterials[**]

In general, the laws of conservation of mass and energy, as well as of physical transport phenomena, provide the framework for reactor calculations. Of course, immobilized biomaterials are *catalysts* which merely influence the rate of reactions without affecting the reaction equilibrium. Immobilized biomaterials often catalyze reactions under mild temperature conditions at a rate that exceeds that of solid, non-biological catalysts. Admittedly, comparable or better rates can be achieved with non-biological catalysts at elevated temperatures, while most biomaterials are denatured above 60 °C. An exception is the enzyme α-amylase (cf. Section 4.2.1).

The strategy for deriving rate expressions in chemical kinetics involves an appreciation of what elementary reactions might be involved in the system of interest. The reaction considered to be the slowest is the rate-limiting reaction, and it provides a reasonable rate expression. However, for immobilized biomaterial kinetics, the starting point most frequently used is a postulation developed in the early 20th Century by *Henri, Michaelis-Menten,* and *Briggs-Haldane,* namely Eq. (1).

$$-\frac{dS}{dt} = v = \frac{kES}{K_m + S} \tag{1}$$

[*] For detailed reviews see [11–16].

[**] The following abbreviations are used:

E Total concentration of biomaterial (enzyme), free and bound
F Flow rate
k Turnover number, a constant whose dimension is a reciprocal of time
K_i Product inhibition constant
K_m Michaelis constant with the dimension of concentration. Its numerical value corresponds to the substrate concentration at half-maximal reaction rate
P Product concentration
S Concentration of the non-bonded substrate at time t
S_0 Initial substrate concentration
S_t Total substrate concentrations if all product were converted to substrate
t Reaction time
v Reaction rate
V_{max} Maximum reaction velocity ($=kE$)
X Fractional conversion, $(S_0-S)/S_0$
X_e X_t at equilibrium
X_i $(S_t-S_0)/S_t$
X_t $(S_t-S)/S_t$

To many, this expression would be recognizable as being similar to that for a hyperbolic function, or Langmuir-Hinshelwood, or Houghon-Watson kinetics. The Michaelis-Menten equation [Eq. (1)] thus expresses kinetics between zero and first order. At low concentrations of the limiting substrate (reactant), the reaction is first order. If the substrate concentration is increased, the reaction order gradually diminishes to zero. There is also a direct dependence of the reaction velocity upon the total enzyme concentration. The parameters in the Michaelis-Menten equation can be estimated by rearranging the equation to yield a linear plot.

$$\frac{1}{v} = \frac{1}{V_{max}} + \frac{K_m}{V_{max}} \cdot \frac{1}{S} \tag{2}$$

Such a plot is referred to as the Lineweaver-Burke plot. Figure 9 is an example for a free as well as an immobilized protease enzyme[17]. That the data for the immobilized form are non-linear suggests mass transport effects, discussed later in this article (see Section 3.3). Other linearized and useful forms of the Michaelis-Menten equation are the Hanes-Woolf, Woolf-Augustinsson-Hofsfee, and Eadie-Scatchard plots.

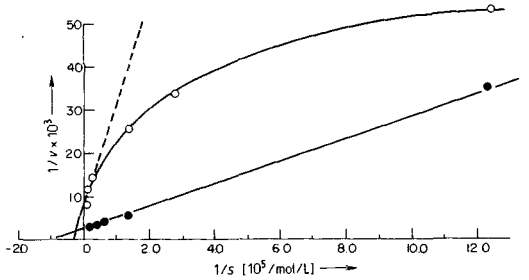

Fig. 9. A Lineweaver-Burke plot for a *B. subtilis* neutral protease with 1 percent sodium caseinate as the substrate. Zirconia coated silica glass was used as the support. The curvature in the plot for the immobilized enzyme indicates mass transfer effects. O—O: immobilized enzyme, $K_m = 3.3 \times 10^{-5}$ mol/L; ●—●: native enzyme, $K_m = 6.2 \times 10^{-6}$ mol/L (after [17]).

More often than not, the kinetic expression is more complex than Eq. (1). Frequently, inhibition or activation by the substrate or the product is observed, or the reaction involves multiple substrates, cofactor activation or multiple products. For immobilized biomaterials in particular, microenvironmental parameters such as pH, temperature and transport resistances are also factors to be considered. In the case of hydrolysis of lactose by β-galactosidase, a product, galactose, acts as an inhibitor. In this case, Eq. (1) may be modified as follows to include product inhibition by product, P:

$$v = \frac{kES}{S + K_m\left(1 + \frac{P}{K_i}\right)} \tag{3}$$

where K_i is the inhibition constant. The lower the value of K_i, the greater is the degree of inhibition (for a given S and P).

Since a knowledge of these kinetic parameters as well as the kinetics is extremely valuable in predicting the behavior of an immobilized biomaterial system, the subject has befittingly received much attention (improvement of kinetic studies, cf. [18–23]).

3.3. Effect of Heat and Mass Transport Resistance

Most reactions catalyzed by immobilized biomaterials have a low heat of reaction. So mass transport and not heat transport resistances happens to be the important consideration. The substrate(s) must be transported to the active site(s) of the attached catalyst and the product(s) away from it. This movement is guided by the rules of diffusion and convection. One should always remember to ensure that kinetic data are so obtained that reaction, and not diffusion, is controlling. In many cases, the kinetics observed are termed "apparent kinetics" when mass transport resistance could be significant. It should be noted, that "apparent K_m" is not an intrinsic property but is a function of the micro- and macroenvironment[24]. It is useful to know if the "intrinsic" or real kinetic parameters of a biomaterial system have changed as a result of immobilization. Such knowledge can be indispensible in the scale-up and design of industrial reactors.

It is convenient to think in terms of external mass transfer effects and internal mass transfer effects. The concern while considering the internal mass transfer has to do with transport resistance inside the porous particle or membrane to which the biomaterial is immobilized. External mass transfer problems involve transport resistances in the media surrounding the immobilized biomaterial particle or membrane. In such studies, chemical engineering concepts for determining controlling resistances in solid catalyzed reactions and for simultaneous diffusion and reaction are relevant[25].

Even when the kinetics for an immobilized biomaterial system can be described by a Michaelis-Menten type pattern, mass transfer effects can cause Lineweaver-Burke type plots to be curved or non-linear (cf. Fig. 9). While a non-linear Lineweaver-Burke plot[17,26,27] is not a definite indication of mass transfer problems, its presence is sufficient cause for a strong suspicion. A number of papers have presented mathematical analyses of non-linearity in such plots[28–31]. Both internal and/or external mass transfer limitation can cause this non-linearity. A significant difference between the K_m values for the soluble and the immobilized biomaterial, even in an otherwise linear kinetic plot[32], is also a suggestion that mass transfer resistances may be present.

The significance of internal mass transfer effects is often expressed in terms of an effectiveness factor η as defined below:

$$\eta = \frac{\left[\begin{array}{c}\text{Apparent or observed reaction rate with porous}\\ \text{particle or membrane}\end{array}\right]}{\left[\begin{array}{c}\text{Reaction rate without internal mass transfer}\\ \text{resistance}\end{array}\right]} \quad (4)$$

Another dimensionless variable that can be used to express the magnitude of the external mass transport effects is the Damköhler number Da:

$$\text{Da} = \frac{\left[\text{Maximum true or intrinsic reaction rate}\right]}{\left[\begin{array}{c}\text{Maximum mass transfer rate of substrate from}\\ \text{bulk to interface}\end{array}\right]} \quad (5)$$

Thus, when η is close to 1, and Da is much less than 1, a system may be said to have low mass transfer resistance and consequently to be relatively free of mass transfer problems. A few practical techniques available for ascertaining whether external mass transfer is a problem will be considered first, to be followed by a few ways of examining pore diffusion problems.

In general, the effect of external mass transfer resistance is to reduce the observed activity. If the apparent reaction rate remains unaffected by a sufficiently large variation in linear velocity, then external mass transfer is not the primary limiting factor in the system being considered. Experimentally, for packed-bed type reactors, considered later in this paper, this can be examined by operating with different bed heights but the same residence time. A more common approach is to measure the reaction rate for a series of flow rates as shown in Figure 10 for immobilized yeast invertase[33].

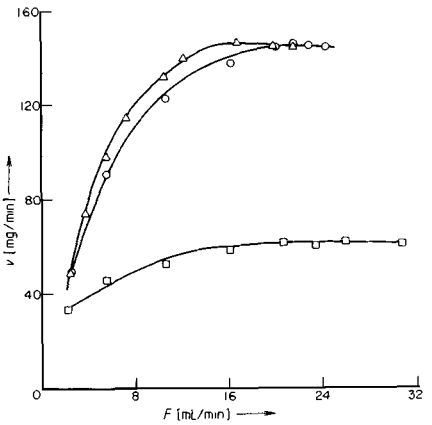

Fig. 10. Examination of external mass transfer effects. Invertase from *C. utilis* was immobilized onto porous cellulose beads. Bead size: □ 28 mesh, ○ 35 mesh, △ 48 mesh. Dependence of the reaction rate v (formation of invert sugar from saccharose) on flow through F (after [33]).

Such studies should be carried out under conditions of negligible internal or pore mass transfer resistance, as would be the case for non-porous supports. Estimates of actual rates of external mass transfer can be made with the help of several mass transfer correlations[12,16,34], originally arrived at in the chemical engineering literature. The external mass transfer rate can be compared with the rate of biochemical reaction to judge the relative importance of external mass transfer. A convenient, short-cut procedure is that of *Satterfield*[35,36]. The height of an immobilized biomaterial bed required to yield the observed degree of substrate conversion, assuming that film diffusion is controlling, can be calculated using *Satterfield*'s correlation. If the actual bed height being used in the system is significantly greater than the calculated bed height, external or film diffusion resistance is insignificant.

Pore diffusion effects, in general, also lower the observed activity as expressed by the effectiveness factor η [Eq. (4)]. A general idea of how significantly pore diffusion can influence reaction rates is provided by Figure 11[37]. As one might expect, the effectiveness factor increases as the substrate concentration increases. The relative increase

and the actual value of η also depend on the modified Thiele modulus Φ_0, a dimensionless number incorporating the shape and site of the biomaterial particle or membrane, the effective diffusivity, and the kinetic constants K_m and V_{max}. Larger particles or thicker membrane means larger Φ_0. For a substrate concentration about ten times the Michaelis constant and for a Thiele modulus of about two, the observed reaction rate is reduced by about 50%.

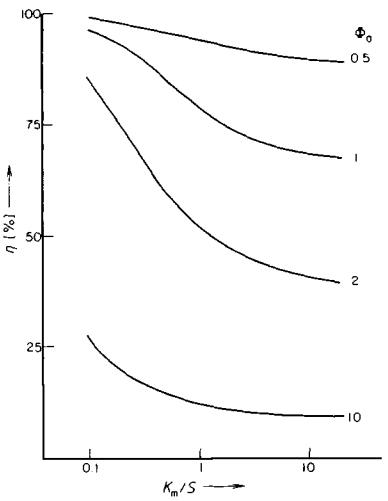

Fig. 11. Relationship between the internal effectiveness factor, η, the Thiele modulus, Φ_0, and dimensionless substrate concentration, K_m/S (after [37]).

As explained by *Levenspiel*[25], the existence of strong resistance to pore diffusion can be determined by at least the following three methods (assuming that resistance to external mass transfer is negligible):

1. *By estimating a value for the effective diffusion coefficient* within the enzyme particle or membrane. Appropriate test criteria[38] can be applied to see if strong pore resistance is present. In addition, the observed rate, the substrate concentration, support measurables, and the rate expression are required. A knowledge of the effective diffusion coefficient also permits one to utilize generalized plots for estimating the effectiveness factor, η[12,16,32]. However, since the estimation of the effective diffusion coefficient is not straightforward, the next two approaches are probably used more often.
2. *By measuring reaction rates for different particle sizes or membrane thicknesses.* If no increase is seen in the observed reaction rate by decreasing the membrane thickness or particle size, pore diffusion problems are not likely to be significant[39].
3. *By measuring reaction rates at different temperatures.* Reaction rates are significantly more temperature dependent than are diffusion rates. Reaction rate *versus* temperature data can be used to estimate an activation energy *via* an Arrhenius plot (see Fig. 12).

A non-linear or curved Arrhenius plot strongly suggests pore diffusion problems. However, a linear Arrhenius plot is only a partial proof of the absence of pore diffusion limitation. For example, for the case of β-amylase immobilized onto porous silica[40], the Arrhenius plot (Fig. 12) is linear. Despite that, the effectiveness factor for this system was estimated to be about 0.2, indicating slow intraparticle diffusion. A comparison between the activation energies (calculated by multiplying the slope of the Arrhenius plot by the ideal gas law constant and changing the sign) for the soluble and immobilized biomaterial also helps one to determine if pore diffusion is a problem[41]. The observed activation energy for an immobilized biomaterial system involving strong pore diffusion limitation is roughly one-half the true or intrinsic activation energy[25] ascertained for the reaction catalyzed by the native biomaterial.

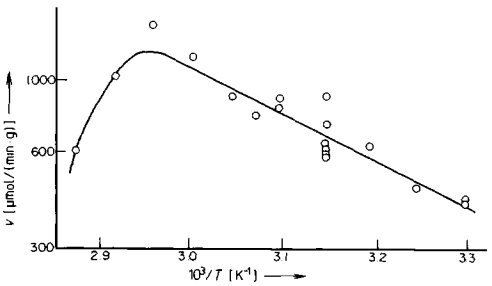

Fig. 12. An Arrhenius type plot for barley β-amylase immobilized onto porous silica particles. Dependence of the reaction rate v (formation of maltose (μmol) from starch referred to immobilized enzyme (g) and time (min)) on the temperature (after [40]).

Another practical method to define conditions where pore diffusion is not significant is the "e-test" suggested by *Yamane*[42]. According to this concept, utilized by others previously, reaction rate measurements with varied biomaterial loadings (amount per unit weight) are made. The data should exhibit a hyperbolic profile (Fig. 13), and the region where the rate increases linearly with loading can be identified for a high effectiveness factor.

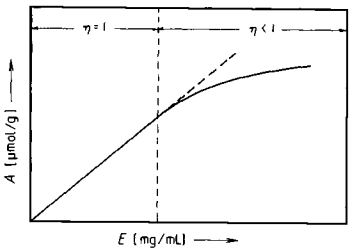

Fig. 13. Determination of the range of an enzyme reaction where the effectiveness factor, η, is equal to 1, assuming the biomaterial concentration itself does not affect the activity loss upon immobilization. Dependence of A (μmol substrate converted per g of immobilized enzyme) on the enzyme loading E (mg protein per mL of solution) (after [42]).

There are several other aspects of the effect of pore diffusion on immobilized biomaterial performance. For a biomaterial strongly susceptible to substrate inhibition, pore transport resistance might actually enhance the reaction. Such behavior has been observed with immobilized xanthine oxidase[43] and immobilized invertase[33]. It has also been suggested that the influence of pore diffusion alone is to enhance the temperature and pH stability of an immobilized biomaterial, *i.e.* the activity *versus* temperature or pH curve is broadened by the diffusion influence[44]. If the substrate molecules and/or the biomaterial support matrix carry a charge, then the electrostatic effects could be sig-

nificant; and the above observation does not apply in the case of pH stability. In such a case, one may instead observe a shift in the optimum pH (cf. Fig. 3).

3.4. Reactors for Immobilized Biomaterial Systems

Before discussing the considerations employed in choosing the reactor type, a brief review of the "idealized" types is in order. Performance equations for three types of "ideal" reactors have been well developed in the chemical engineering literature[45]. These three are: the batch reactor, the plug-flow reactor (also known as the slug flow, piston flow, ideal tubular and unmixed-flow reactor), and the mixed-flow reactor (or the back mix, the ideal stirred tank, the continuous flow stirred tank reactor or the CFSTR) (Fig. 14).

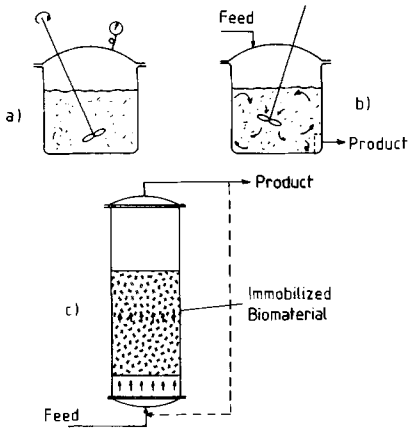

Fig. 14. Idealized reactor types: a) the batch reactor, b) the continuous flow stirred tank reactor, CFSTR, and c) the fixed bed reactor.

A fourth type, generally considered a hybrid of the plug-flow and the mixed-flow reactors, is the fluidized-bed reactor (Fig. 15a). In ideal plug flow, the substrate passes through the reactor as a slug, without any mixing with other slugs ahead or behind. In ideal mixed flow, the reactor substrate concentration is uniform throughout and is the same as the outflow substrate concentration. The flow pattern in a fluidized bed is not described as easily.

In a way, the fluidized-bed reactor, in which the immobilized biomaterial particles become suspended in an upward flowing substrate stream, is a "real" reactor. For preliminary experimental work, a differential recycle reactor (Fig. 15b), which allows a packed bed to be used in conjunction with a well-mixed reservoir of the feed and the product, is effective[25] and has been used extensively[46-49]. Most real reactors behave neither exactly like a plug-flow reactor nor like a CFSTR. However, once a particular real immobilized biomaterial reactor is judged to behave somewhat similar to an ideal reactor, performance equations can be derived from a knowledge of the material balances and the kinetics of the system. This can be an excellent starting point. Actually, the flow pattern of a real reactor can be analyzed by injecting at the inlet of the reactor a non-reactive tracer, and measuring the tracer concentration at the outlet as a function of time[50,51].

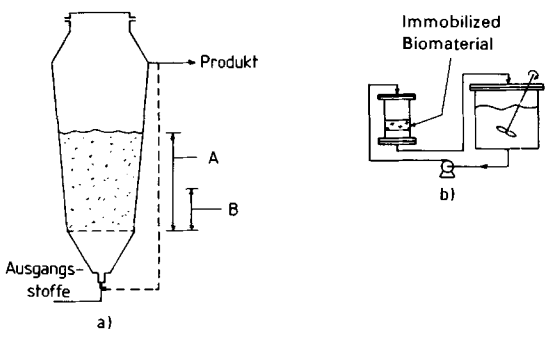

Fig. 15. a) The fluidized bed reactor, A: expanded bed, B: non-fluidized bed; b) differential bed recycle reactor.

The reactor performance equations applicable to the real immobilized biomaterial system of interest are one of the pivotal points of information during its development. Among other things, these equations permit an estimate of the biomaterial activity in the reactor at a given point in time. Often, it is desirable to arrange to have the reactor behave similarly to either the plug flow or the mixed flow, depending upon the kinetics. Performance equations for the batch, plug-flow, and the mixed-flow reactors, for modified or simple Michaelis-Menten kinetics, have been listed in several reviews[11-16,52]. Eq. (6) is valid, *e.g.*, for a plug-flow system exhibiting product inhibition, as is the case in the hydrolysis of lactose by immobilized lactase:

$$\frac{kE}{F} = S_0\left(1-\frac{K_m}{K_i}\right)(X_t - X_i) - \left(K_m + \frac{K_m S_t}{K_i}\right)\ln\left(\frac{1-X_e}{1-X_i}\right) \qquad (6)$$

3.4.1. Choice of Reactor Type

Perhaps somewhat facetiously, it may be said that *one wants the highest activity per unit reactor volume* (hence the least processing cost), *for the longest possible duration*, from an immobilized biomaterial reactor. One of the main advantages in immobilizing a biomaterial, as mentioned earlier in this article, is its convenient reuse. So in principle, any "closed"[15] system that would permit the biomaterial to be reused, at the same time yielding an "acceptable" degree of substrate conversion for an "acceptable" length of operating time is "acceptable". Some factors that influence the choice of reactor type are listed below:

1) Nature of the biomaterial support
2) Nature of the substrate to be processed
3) Reaction kinetics
4) Cost of reactor construction and operation
5) Ease of reactor scale-up
6) Method of regeneration or replacement of the immobilized biomaterial
7) Operational stability and requirements
8) Activity per unit volume or productivity required

Operational requirements should, of course, influence the reactor or system design. If pH or dissolved oxygen control is required, the well-mixed reactor may be favored.

This is because a direct addition of acid/base or a gas is easily possible. It should be pointed out that a fixed-bed reactor in conjunction with a recycle flow loop will allow acid/base/gas control external to the reactor. In a fixed-bed reactor, one has to be concerned with compressibility of the bed at high flow rates. Similarly, physical disintegration or solubilization of the support and/or the biomaterial may be an issue in any type of reactor under consideration.

One requirement that is very common to the immobilized biomaterial reactor system is that of microbial contamination control. In some cases, one may have to operate a sterile system. While that means the use of numerous precautions during the reactor operation, it also means the systems have to be sterilized. If autoclaving is the method chosen for sterilization, then the system components have to be capable of withstanding autoclave conditions (121 °C steam for 15 min to a few hours). In some cases, it may just not be practical to operate a sterile system. In that case, the operating protocol has to try to minimize the effects of unwanted microbial contaminants.

While it is generally perilous to generalize, a few comments concerning some features of the various reactor types (Table 2) will be made here. The Michaelis-Menten

Table 2. Reactor types and characteristics [11–16, 53].

Type	Comments
Batch (Fig. 14a)	Convenient to set up and operate. More efficient than a CFSTR for reaction kinetics of an order greater than zero.
Fixed bed, continuous (Fig. 14c)	Convenient and preferable for systems with kinetics of an order greater than zero, and for systems exhibiting product inhibition. Support material should have good particle strength and rigidity. Mass transfer problems can be a handicap for large carrier particles. Pressure drop can be a problem for small carrier particles.
Well-mixed, and fluidized bed (Fig. 15a)	Can handle feeds containing particulates; well mixed is preferable for systems exhibiting substrate inhibition; useful in circumventing mass transfer problems; support should have high abrasion resistance; scale-up of fluidized beds not well known.
Fixed or fluidized bed with recycle (cf. Fig. 15b)	Can be operated under conditions approximating plug flow at low or zero recycle; CFSTR behavior may be approached by operating at high recycle rates.

expression, with or without appropriate modifications, and material balances offer us a tool to estimate the packed-bed or well-mixed reactor volume required for a given degree of substrate conversion. The very nature of the Michaelis-Menten equation suggests that, for systems deviating not too significantly, it would be more efficient to have a reactor operate at substrate concentrations as high as possible relative to the K_m. This is the case in plug flow. On the other hand, in a well-mixed reactor, the substrate concentration is in effect diluted due to back mixing. Quantitative comparisons based on the kinetics and material balances clearly indicate that if a high degree of substrate conversion is desired, plug-flow operation is significantly better than well-mixed flow[11-16,54]. For obvious reasons, if a product formed in the system inhibits the reaction, the plug-flow reactor shows even greater promise. In general, a plug-flow reactor may also be expected to operate at a higher effectiveness factor than a well-mixed reactor at a given substrate concentration. However, for systems exhibiting severe substrate inhibition, backmixing is helpful as it would keep the reactor substrate concentration low. Then, a well-mixed reactor should be considered.

Conceptually, a fluidized-bed reactor offers a solution to some problems possible with fixed-bed, or plug-flow reactors. Smaller particles can be used to minimize mass transport resistance without significant plugging problems, and high biomaterial loadings per unit weight of the carrier can be employed. A fluidized-bed reactor can be operated so as to approach plug-flow behavior. The pressure drop in a fluidized-bed reactor, on the other hand, can be significantly less than a packed bed operated at a comparable flow velocity[54,55]. Until recently, workers in immobilized biomaterial catalysis tended to avoid working with fluidized-bed systems. Uncertainties in scaling-up and the difficulty of developing proper performance equations[56] may have played a part in this. Recently, however, pilot scale studies using a fluidized-bed system have been performed by *Coughlin et al.* for lactose hydrolysis[57] and corn starch hydrolysis[58], by *Tsao et al.* for glucose isomerization[59], and by *Emery* and *Cardoso* for soluble starch hydrolysis[51].

Among the well-known commercial scale applications of the plug-flow, fixed-bed system are: the production of High Fructose Corn Syrup or Isoglucose (HFCS or IGS) by the Clinton Corn Processing Co. and Corn Products International in the United States, and the Novo Industri A/S, Denmark, as well as amino acid production by the Tanabe Seiyaku Co., Japan. Mainly due to operational requirements, such as tight pH control, the well-mixed reactor has been used commercially by Beecham Pharmaceuticals, Squibb, and Astra AB for the acylation of benzylpenicillin by immobilized penicillin acylase[60]. Snamprogetti of Italy has employed lactase and penicillin acylase, entrapped in cellulose triacetate fibers, in both the well-mixed and the plug-flow arrangements[60]. The commercial fixed-bed reactors appear to be in the 1–9 m^3 (35–315 ft^3) range with bed diameters usually under 1.5 m (5 ft)[60]. The support material particles tend to be in the 0.2 to 4 mm range. Typical pore morphologies for porous inorganic carriers have been presented earlier (see Fig. 7 and 8).

Several other interesting types of reactors are awaiting commercial exploitation. These include reactors using membranes in tubular or rolled form[16,61], inorganic supports in the monolith form[62], and those employing magnetizable particles as the support material[63,64]. Reactors containing membranes rolled in a spiral offer a high surface area per unit volume and good substrate-biomaterial contact. Magnetizable particles, of course, permit fluidized bed operation with minimal loss of the immobilized biomaterial. Another promising development in Japan[65] has been that of biomaterial immobilization on polyvinyl alcohol fibers making available very high surface-to-volume ratios.

3.5. Operational Stability

Although not the only one, a critical parameter examined during the development of an immobilized biomater-

ial system is its operational stability. It may be emphasized here, that operational stability implies just that, *i.e.* stability when the system is under operation for its intended application (Fig. 16). Operational stability is to be distinguished from storage stability, *i.e.* stability when the immobilized biomaterial preparation is periodically tested for its activity while under storage. If available, information on operational stability is by far the more useful. Operational stability is usually expressed in terms of a half-life, $t_{1/2}$, which is the time elapsed during a 50% decline in activity. The causes of this decline in activity may be one or more, and the common ones are listed in Table 3. For comparison purposes, advantage is commonly taken of the fact that the decline in activity of an immobilized biomaterial often follows an exponential decay pattern. This permits a straight line fit between the logarithm of activity and time for data of the type of Figure 16. Frequently, an initial drop in activity due to a washout of the loosely bound biomaterial, or an initial increase due to some activation by a feed component, are observed.

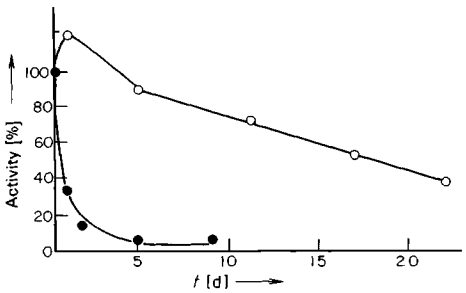

Fig. 16. Operational stability of immobilized aminoacylase for a relatively high concentration of the substrate (0.6 mol/L acetyl-DL-methionine) as a function of time. ●—●: tannin-aminohexylcellulose support; ○—○: DEAE-Sephadex support (after [94]).

Table 3. Possible factors affecting the operational stability of immobilized biomaterial systems.

Microbial growth
Desorption or leaching
Inactivation by trace metals or other inhibiting materials present in the feed
Coating of the biomaterial particle or membrane by proteins or other foreign materials
Thermal denaturation
Physical instability of the support material to withstand dissolution, attrition *etc.*
Variations in temperature and pH

As pointed out by *Pitcher*[66], operational stability studies should be performed as early as practical, with a feed as close as possible to that projected for commercial use. Half-lives could range from two days to over 100 days (in the case of immobilized lactase[66]) depending on the feed composition.

3.6. Processing Costs and Operating Strategy

The central concern in an industrial immobilized biomaterial system is the processing cost per unit of product, assuming major technical questions have been answered. At least a preliminary estimate of the processing cost can be made without much difficulty by including reasonable costs of the major components (Table 4). If possible, this should be followed with a sensitivity analysis to see how the processing cost is affected by the various components. Among the few cost estimating examples in the literature on immobilized biomaterials are those for lactase[67], glucoamylase[58,68], and penicillin amidase[101]. Overall conclusions for amino acid production at Tanabe Seiyaku Co., Japan, have been published[69] indicating that substantial savings were achieved *via* immobilization.

Table 4. Major cost components in an immobilized biomaterial system.

Raw materials including feed
Feed pretreatment, if any
Immobilized biomaterial
- support material
- amount of biomaterial required based on the efficiency of immobilization
- labor and materials required for the immobilization step
- replacement or regeneration of the immobilized biomaterial based on the operational stability
Product preparation
Labor, supervision and maintenance
Depreciation, taxes and insurance

While developing an immobilized biomaterial system, one may be able to arrive at a minimum half-life required for the system to be attractive. It should be possible to estimate the productivity per half-life, incorporating the actual level of biomaterial activity or loading. Thus, if one could significantly enhance the initial activity per unit reactor volume, a shorter half-life may be acceptable. It may be noted here, that doubling the initial activity may not double the reactor productivity[70a] and may increase the pressure drop problems[71]. The relative increase in biomaterial cost will depend on how the efficiency of immobilization varies in the range of interest.

The processing costs can be minimized by maximizing the production rate (the amount of product per unit time). This must be achieved within any constraints on temperature, pH, production rate, product quality, the number of half-lives for which a reactor may be operated, and the number of reactors available. The question of optimal op-

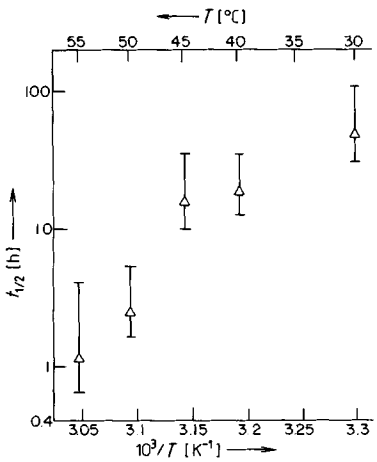

Fig. 17. Operational stability as a function of operating temperature for hog kidney mutarotase immobilized onto porous silica particles. The data indicate that the mechanism of activity decay is different for temperatures below and above 45 °C (after [70b]).

erating strategy in the face of such limitations has been addressed by *Pitcher*[12, 13, 66]. He has shown that given a knowledge of the effect of temperature and flow rate on reactor activity and half-life (Fig. 17), specific and practical operating strategies can be devised. Advantage can be taken, for example, of staggered start-up or regenerating schedules. Even more practical, an approach to maintaining the product quality or the extent of reaction, despite a gradual decay in the immobilized biomaterial activity, is to raise the operating temperature and/or to decrease the feed-flow rate[66, 72]. For any system under commercial development, the availability of the support as well as the biomaterial, in sufficient quantity and at an acceptable price and duration, must also be considered.

3.7. Health and Regulatory Aspects

In the application of immobilized biomaterial systems, health and regulatory considerations have been completely neglected in the literature. This is likely to change as more and more industrial applications are attempted. The following discussion is an admittedly incomplete representation of the many and complex aspects involved in assessing the safety of an immobilized biomaterial.

Enzymes, being proteins, can cause allergic reactions. Some enzymes, especially proteases, can have a non-allergic but highly noxious effect on people. In a skin prick test with papain on an allergic patient, *Flindt*[73] reports a 1 cm weal and 3 cm flare when only 0.3 nanograms of papain were introduced. He also reported a death by an asthma attack when a kilogram of papain powder was spilled into a protein hydrolysis pan, some ten meters from the victim. Thus, precautions will be required of workers to control hazards due to proteinaceous materials causing allergic reactions.

The support material and the chemical reagents, used for the immobilization of a biomaterial, must be proven to be safe unless already held so by the law. If the intended application is in the food or drug area, this demonstration may require considerable expense and effort. Animal feeding studies may have to be conducted. In this regard, biomaterials immobilized by adsorption onto "generally recognized as safe" (GRAS) substances will have an edge. Unless it is considered safe[74, 75], the absence of the enzyme from the product would, of course, have to be verified. Similarly, if microbial growth in the immobilized biomaterial system is a problem, and it is almost a perennial one, any biocides used should be legally considered safe for humans. A few reports on efforts at developing a practical system include information on control of microbial growth by sanitizing agents[76–78]. Sanitization procedures may also affect the system's half-life, *i.e.* enzyme deactivation or carrier deterioration are possible.

4. Applications of Immobilized Biomaterial Systems

4.1. Introduction

The objective of this section is to give the reader a perspective of the state of this technology. No attempt will be made to cover specific research efforts and their details for various applications. References may be consulted, if there is further interest. Keeping this in mind, the applications will be considered in three broad categories:

1) Commercial scale applications and those nearing commercial exploitation,
2) Applications which have been examined on a pilot scale,
3) Laboratory or research scale and potential applications.

Table 5 lists the firms using immobilized biomaterials on an industrial scale.

Table 5. Companies employing immobilized biomaterials on the industrial scale. Abbreviations: Pen. = penicillin, GI = glucose isomerase; Gal = galactosidase.

A. B. Astra (Pen. acylase)
A. E. Stanley Manufacturing Co. (GI[a]) [a]
American Maize (GI) [a]
Amstar Corporation (GI) [a]
Beecham (Pen. acylase)
CarMi (GI) [a]
Central Dairy of Milan (β-Gal) [a]
Clinton Corn Processing, a div. of Standard Brands (GI)
Corn Products International (GI) [b]
Gist Brocades NV (GI) [a]
Great Western Sugar Co. (α-Gal) [a, c]
H. J. Heinz Co. (GI) [a]
Imperial Chemical Industries (GI) [a]
Kyowa Hakko Co. (Fumarase)
Novo Industry, A/S (GI)
Squibb (Steroid dehydrogenase)
Snamprogetti (β-Gal, pen. amidase, hydantoinase)
Tanabe Sieyaku Co. (Aminoacylase, Aspartase, Fumarase, Pen. amidase)
Toyo Jozo Co., Ltd. (Pen. amidase)

[a] Licensed from another company. [b] Licensed from Corning Glass Works. [c] Mycelial pallets containing α-galactosidase (melibiase) activity.

4.2. Commercial and Near-Commercial Applications

4.2.1. Production of High Fructose Corn Syrup[70, 71, 79–86]

A technology spurred by high sucrose prices in the early and mid-seventies, and now shackled by the low sucrose prices, is that of making "Isoglucose", "High Fructose Corn Syrup", or "High Fructose Glucose Syrup". It is perhaps the most significant and splendid commercial example of immobilized biomaterial technology. The enzyme glucose isomerase converts, far more specifically than its chemical alternative, aldo sugars into their keto isomers.

$$\text{D-glucose} \xrightarrow[\text{isomerase}]{\text{Immobilized glucose}} \text{D-fructose}$$

D-fructose competes with sucrose and can be 1.75 times as sweet as sucrose depending on the fructose concentration. The sweetness of HFCS can be varied by changing the fructose/glucose ratio without altering the calorie content. Canned fruits, carbonated and fruit-flavored beverages are some of the products that use the HFCS, which resists microbial growth by virtue of its high osmotic pressure. Syrups containing up to 90% fructose, on a dry basis, are commercially available in the United States.

HFCS technology has been a scene of intense industrial interest as evidenced by the patent activity[86]. Development efforts have not only been directed at improving the enzyme-based process, but also at using intact or

whole cells containing the enzyme[87]. Another improvement has been the availability of an α-amylase, from Novo Industries, which can withstand temperatures up to 105 °C for the initial 5—6 minutes during the starch liquifaction.

The United States estimate for 1979 was 1.6 million tons of HFCS[82]. The production in Europe was about 70000 tons in 1976, less than 1% of the sugar consumption in the EEC. As noted by *Barfoed*[82], the sugar surplus in the EEC, the lifting of a subsidy in 1977 on grain used for HFCS manufacture, and an additional production levy of about $69/dry ton during 1977—79 have virtually stalled the development of this technology in Europe. On the positive side for the HFCS makers in the EEC, an export subsidy was decided upon by the European commission[83].

Thus, immobilization of glucose isomerase has significantly reduced the cost of producing a sweetner from starch—the cost being low enough to completely change the sweetner market. Advantages, like decreased reactor volume, lower costs of adjustments in the product and the feed for the process, and, of course, lower enzyme costs, have played a significant role.

4.2.2. Production of L-Amino Acids[89–100]

The production of L-amino acids is big business worldwide because of their utilization for medicinal and food purposes. About 300 million dollars worth were produced in Japan alone in 1976[88,89]. Amino acids can be produced by isolation from protein hydrolyzate, by fermentation, or by chemical synthesis. The immobilized biomaterial technology has made chemical synthesis a viable option. Chemical synthesis yields an optically inactive racemic mixture of the L- and D-isomers of amino acids. Only the L-form can be incorporated into proteins; and, therefore, being the desired product, it has to be recovered from the racemic mixture. The Tanabe Seiyaku Co. has employed immobilized aminoacylase, since 1969, for this resolution step. This is also believed to be the first industrial application of an immobilized enzyme world-wide. In a continuous automatically controlled process, the racemic mixture of an amino acid is first acylated, then subjected to asymmetric hydrolysis by immobilized aminoacylase. A mixture of acyl-D form and the L-form of the amino acid is obtained, and the two can be separated because of solubility differences. The acyl-D form is racemized and reused.

Tanabe Seiyaku Co. has produced amino acids such as methionine, phenylalanine, alanine, tryptophan and valine on a large scale. Production of others such as L-Dopa, phenylglycine and hydroxyphenylglycine is said to be planned. Results from the extensive development studies on the immobilized aminoacylase system have been well documented by *Chibata et al.*[90–93].

The system employs *Aspergillus oryzae* derived aminoacylase, immobilized onto DEAE-sephadex by ionic binding in a packed-bed reactor. The DEAE-sephadex has proven to be stable over at least seven years of use.

Additional economies in immobilized aminoacylase utilization may be possible based on a recent report from Tanabe Seiyaku[94]. Laboratory scale studies have shown that a substrate three times more concentrated may be processed using a newer method of immobilization, *i.e.* adsorption onto tannin covalently bound to aminohexylcellulose (cf. Fig. 16).

Snamprogetti S.P.A. in Italy has achieved pilot scale application of immobilized aminoacylase for the production of L-tryptophan[95]. In their batch-recycle reactor system, the enzyme is not immobilized *per se*, but entrapped in cellulose triacetate fibers. Snamprogetti has also produced D-amino acids from hydantoins using a similarly entrapped calf liver enzyme[96].

For one amino acid, L-aspartic acid, the Tanabe Seiyaku Co. has found that using intact or whole cells in immobilized form is preferable to using the isolated aspartase enzyme. In their process, used commercially since 1973, the aspartase activity of *Escherichia coli* cells entrapped in a polyacrylamide gel catalyzes the formation of L-aspartic acid from ammonium fumarate[97].

$$\text{Fumaric acid} + \text{ammonia} \xrightarrow[\textit{E. coli}\ \text{cells}]{\text{Aspartase in Immobilized}} \text{L-Aspartic acid}$$

A striking feature of the immobilized biomaterial technology has to do with activation and inhibition of the biomaterial activity, in some cases with extraordinary significance. The entrapped cells exhibit an order of magnitude increase in activity from 130—180 to 1200—1700 moles per hour per mL of gel, when incubated in the substrate containing magnesium ions for 24—48 h at 37 °C. The system, employing a 1000 L packed-bed reactor, has excellent stability, about 120 d at 37 °C; and the product yields are in the 90—95% range. The exothermic reaction, causing a 6 °C increase for a 1 M substrate concentration, necessitates the reactor having a provision for heat removal.

Recently *Chibata et al.*[98] have reported an improved *E.-coli* immobilization scheme for L-aspartic acid production with carrageenan, a polysaccharide used as a gel-forming additive in foods, as the support material. The cells, following entrapment in the gel, are cross-linked with glutaraldehyde and hexamethylenediamine. Although the projected half-life of a laboratory scale column was 686 days, the stability after scale-up was still to be studied.

Production of two amino acid derivatives, L-citrulline[99] and glutathione[100], has also been studied at Tanabe Seiyaku. The glutathione production, based on entrapped *Saccharomyces cerevisiae* cells, was accomplished with continuous regeneration of the co-factor ATP. A continuous production of L-citrulline from L-arginine employed polyacrylamide gel entrapped *Pseudomonas putida* cells in a packed-bed reactor. A half-life of 140 days at 37 °C for the L-arginine deaminase activity in the laboratory scale reactor was observed. Although the optimum temperature was reported to change from 37 °C to 55 °C, this observation may well depend upon the conditions of the assay for activity.

4.2.3. Production of 6-Aminopenicillanic Acid

Another field where the immobilized biomaterial technology has had its impact is in the manufacture of semisynthetic penicillins. An important intermediate, 6-aminopenicillanic acid (6-APA), has been produced commer-

cially or at least on a pilot scale in Italy[101], Japan[102,103], Sweden[104], England, and the USA[60].

$$\text{Benzylpenicillin} \xrightarrow[\text{Penicillin Acylase}]{\text{Immobilized}} \text{6-APA} + \text{Phenylacetic Acid}$$

The stability of the enzyme, penicillin acylase or amidase, is significantly improved by immobilization. This coupled with the fact that the immobilized enzyme deployment in this case means lesser impurities in the product, is an explanation of the industrial interest in this technology.

Penicillin acylase covalently bonded to Sephadex G-200 is employed in the scheme used since 1973 at AB Astra, Sweden. Covalent binding onto Amberlite beads is used in the Beecham process. Both these companies and Squibb use a batch, stirred tank reactor mainly due to the operational requirement of alkali addition for pH control. Denaturation of the immobilized penicillin acylase by the alkali, unless its addition is controlled carefully, can be a problem resulting in low operational stability[105].

4.2.4. Production of Other Organic Compounds

Organic compounds such as L-malic acid and urocanic acid have been manufactured in Japan by exploitation of the immobilized biomaterial technology[88,106-109]. L-Malic acid, used in intravenous infusion mixtures and for treatment of hepatic ailments like hyperammonemia, is produced by the Tanabe Seiyaku Co. and the Kyowa Hakko Co. Urocanic acid, a sun-screening agent, is manufactured at Tanabe Seiyaku.

$$\text{Fumaric Acid} \xrightarrow[\textit{Brevibacterium ammoniagenes}]{\text{Fumarase in immob.}} \text{L-Malic Acid}$$

$$\text{L-Histidine} \xrightarrow[\text{in immob. } \textit{Achromobacter liquidum}]{\text{L-Histidine ammonia lyase}} \text{Urocanic Acid} + NH_3$$

The Tanabe Seiyaku studies reveal a problem characteristic with using intact or whole cells rather than the biomaterial in its isolated form. Immobilized whole cells often have bioactivity other than the one desired. In the case of L-malic acid the immobilized *B. ammoniagenes* cells contained the unwanted activity to form succinic acid in addition to the malic acid. Fortunately, it was found that suspending the polyacrylamide gel entrapped cells in substrate solution containing detergents such as deoxycholic acid or bile acid, not only suppressed the succinic acid formation it also enhanced the fumarase activity 6—7 times. Similarly, while *A. liquidum* cells were otherwise suitable for urocanic acid production, they also had urocanase activity. Thus, uroconic acid formed was further converted into oxoimidazolepropionic acid. In this case, heating the cells for 30 minutes at 70 °C eliminated the urocanase activity.

Another not too uncommon feature of immobilized biomaterial systems is the effect of metal ions on their stability (see Section 4.2.2). The inclusion of Mg^{2+} (1 mmol/L) improved the *A. liquidum* system half-life to an estimated 6 months, relative to 15 days for feed containing no Mg^{2+}[109].

4.2.5. Hydrolysis of Whey and Milk Lactose

Immobilized biomaterial technology appears poised to offer the dairy industry a new product *opportunity* out of the *problem* of whey utilization. It is estimated that nearly 35 million tons of whey is produced annually worldwide. Much of the sweet whey, from the manufacture of hard cheeses, is presently dried and blended in some animal and human processed food products. Utilization of acid whey, a by-product from the manufacture of soft cheeses like cottage cheese, on the other hand, poses a problem due to its acidity. The percent utilization of whey varies from about 60 percent in the US and Canada, and about 75 percent in France and the USSR, to about 95 percent in Denmark and Holland[110a]. This may leave as much as 10 to 12 billion pounds in the US that is not properly utilized. Because of its high biochemical oxygen demand and pollution regulations, most of the processed whey is either dried or concentrated. However, the increasing energy prices continue to have impact on the drying costs. Thus, the incentive to find a profitable way to upgrade the whey and improve its utilization is obvious.

Whey contains 4.5 to 5 percent lactose, 0.5 to 0.8 percent protein and about 0.7 percent salts. So the major components of commercial value are lactose and protein. The protein can be separated by ultrafiltration. As shown in Table 6, the sweetness of the permeate is significantly improved if the lactose could be hydrolyzed. This whey lactose utilization can be performed by an immobilized biomaterial (discussed here), or on a catalytic resin[112]. Other alternatives studied have been that of fermentation to make alcohol and methane[110a] and crystallization of lactose before protein recovery[110b].

Table 6. Relative sweetness of some sugars in 10% aqueous solution [111].

Sugar	Relative sweetness
Sucrose	100
Lactose	40
Glucose	75
Galactose	70

Immobilized lactase (β-galactosidase) can be used to hydrolyze lactose to glucose and galactose, thereby improving the sugar solubility in addition to sweetness. The hydrolyzed whey can then be used for its sweetness and nutritive qualities in dairy products. The hydrolyzed whey may also be used as a fermentation substrate for making baker's yeast[110c]. Figure 18 shows the process scheme of a system offered by Corning Glass Works.

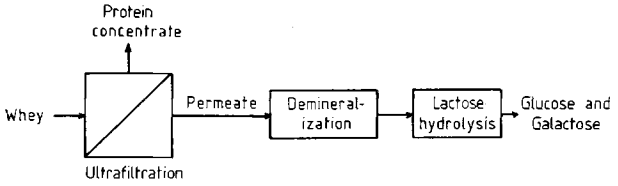

Fig. 18. A scheme for whey utilization. The protein is recovered by ultrafiltration and a sweetner is produced by hydrolyzing the demineralized permeate with immobilized β-galactosidase.

Demineralization of the permeate *via* ion-exchange or electrodialysis reduces the "salty" nature of the hydrolyzed syrup. The system employs a packed bed reactor in the down flow mode. The fungal lactase is immobilized onto 30/45 mesh controlled pore silica beads by chemical coupling using the aqueous silane-glutaraldehyde method. A pilot scale, fluidized bed reactor system was developed by *Coughlin et al.*[116,117] at Lehigh University in the United States. Development studies from Corning Glass Works and others on whey lactose hydrolysis have been documented in the literature[67,77,113-119].

A related problem is that of milk lactose hydrolysis for lactase deficient people. A 10 ton per day commercial plant for the hydrolysis of lactose in skim milk, based on a process developed by Snamprogetti, is in operation at the Central Dairy of Milan, Italy[78,120,121]. The enzyme, a yeast lactase, is entrapped in spun cellulose triacetate fibers and the fibers placed in a jacketed column. The fibers are first washed with sterile buffer and then lactose hydrolysis is carried out by batch recirculation of sterile, skim milk. The product "latte accadi" is said to have a pleasant sweetness and good shelf-life.

4.2.6. Analytical Applications

Analytical applications of immobilized biomaterials are many[122,123], but only mention of the successfully commercialized examples will be made here. Glucose analyzers, based on immobilized biomaterials, are marketed by Yellow Springs Instruments (YSI), Yellow Springs, Ohio; Technicon Instruments, Tarrytown, New York; and Leeds and Northrup Co., North Wales, Pennsylvania, from the US, and Radiometer Instruments, Copenhagen, from Europe. An instrument for the analysis of urea nitrogen in blood, employing immobilized urease, has been developed by Owens-Illinois[80].

The analyzer from YSI[124-127] can be utilized for a variety of analyses, depending upon which immobilized enzyme is used. As an example, glutaraldehyde coupled enzyme glucose oxidase is utilized to produce H_2O_2.

$$\beta\text{-D-Dextrose} + O_2 \xrightarrow[\text{glucose oxidase}]{\text{Immobilized}} H_2O_2 + \text{D-Glucono-}\Delta\text{-lactone}$$

The current flow is proportional to the H_2O_2 concentration. Sucrose can be analyzed by using a membrane containing immobilized invertase, mutarotase and glucose oxidase which together help to produce H_2O_2 from sucrose. Similarly, lactose can be analyzed when a membrane containing immobilized galactose oxidase is utilized.

Whichever immobilized enzyme(s) is utilized, the enzyme membrane is actually sandwiched between a cellulose acetate membrane (molecular weight cut off 100) and a polycarbonate membrane (0.03 micron pores). The former passes H_2O_2 but excludes other reducing agents which might be present in the sample. The polycarbonate membrane excludes unwanted cells or enzymes from the reaction zone (Fig. 19).

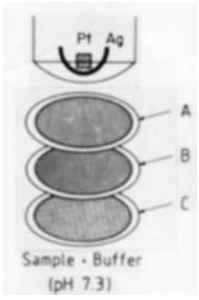

Fig. 19. A schematic representation of an analyzer based on immobilized biomaterials (Yellow Spring Instruments, USA). The immobilized enzyme membrane to be used depends on the analysis desired. The immobilized enzymes available and their intended applications (in parentheses) are: glucose oxidase (glucose analysis); invertase, mutarotase and glucose oxidase (sucrose analysis) and galactose oxidase (lactose analysis). A: cellulose acetate membrane, molecular cut off 100; B: membrane with immobilized enzyme(s); C: polycarbonate membrane 5 μm, pore diameter 0.03 μm.

4.3. Production of Glucose from Liquified Starch

An obvious temptation to use immobilized biomaterial technology exists in the saccharification of starch. In theory, an immobilized glucoamylase (amyloglucosidase) could be employed in the HFCS processes, in corn syrup production, or in the making of some alcoholic beverages. Soluble glucoamylase is used in these processes and its sales account for about 14 million dollars in the USA[128] and about 4 million dollars in Japan. At least three pilot scale studies with immobilized glucoamylase have been reported in recent years. The first[129] was based on a fixed bed process, while the other two[51,58] have examined fluidized bed operation. The latter two represent an advancement by virtue of evaluating the kinetics and operation of a pilot scale, fluidized bed immobilized biomaterial system. Although the list below is incomplete, a few key obstacles in the commercial development of this technology are mentioned.

1) Operational Stability: Microbial growth is a serious concern during the operation of immobilized glucoamylase systems. This is because the temperature range for stable enzymatic activity is usually around 40 to 45 °C, also favored by contaminating microbes. A continuous sterile operation at the plant scale is very difficult to maintain. A thermophilic glucoamylase may be the answer.
2) Costs: The cost per pound of the immobilized glucoamylase would have to be almost unrealistically low to replace the existing low cost soluble enzyme use. *Allen et al.*[58] estimate the total processing cost with a fluidized bed system to range from 42 to 62 cents per 100 pounds of solids, relative to 55 to 63 cents for the soluble enzyme process.
3) Yield: A commercial immobilized glucoamylase system would have to yield comparable product quality to the soluble enzyme process. The desirable range for corn processors, 94 to 97 DE, has been difficult to attain in continuous operation with the immobilized biomaterial.

Overall, in this case, the immobilized biomaterial performance and economics must be dramatically superior to justify change at the commercial scale. A possible exception would be the situation where the soluble enzyme must be removed after use and must not be present in the final product for regulatory or health reasons such as in the manufacture of low calorie beers.

5. Summary and Outlook

Perhaps the initial enthusiasm accorded the immobilized biomaterials in the nineteen sixties was somewhat exaggerated. Nevertheless, when one considers the variety of applications that have been examined at the research level and the continuing interest in this technology, a slow but steady growth in real applications can be predicted. A very brief account of the possibilities will be made here.

A statement must be made on the tremendous potential this technology offers with respect to renewable resource utilization (Table 7). To date, considerable work has been accomplished in the USA, the USSR, and other countries on the enzymatic hydrolysis of cellulose. In this case, the substrate cellulose can be considered to be the carrier as well as the substrate for the cellulases because the enzymes and the cellulose form a tight complex. Additional work in this area offers the promise of fuels and chemicals.

Table 7. Some potential applications of immobilized materials.

Utilization of renewable resources
Cofactor regeneration and synthesis
Production of maltose from starch
Disinfection of gaseous streams
Destruction of H_2O_2 in cold milk sterilization
Production of L-lysine from ε-aminocaprolactam
Milk coagulation
Production of cyclodextrin from starch
Flavor modification of ultra-high-temperature (UHT) processed milk
Steroid transformations
Waste conversion

That future practical systems should be capable of exploiting the benefits of co-immobilization seems reasonably clear. Co-immobilization of two or more biomaterials has an enourmous potential because of the synergistic effects that are possible.

This synergy may take many forms. Sequential reactions, protection from inhibitors, enhanced reaction rates, improved pH or thermal stability are only some of the obvious possibilities. One such example is co-entrapment of β-glucosidase and *Saccharomyces cerevisiae* in alginate for converting cellobiose and glucose into ethanol in a fluidized bed reactor[130]. In their bench scale studies, the authors obtained complete conversion to ethanol at dilution rates of about 0.25 per hour.

Improved thermal stability was the result when an alcohol dehydrogenase was co-immobilized with the coenzyme NAD(H) in agarose in another laboratory study[131]. The half-life improved from only a few minutes to just under 2 hours. Further work[132] in the same laboratory in Sweden has verified that the transition temperature, as observed by differential scanning colorimetry, is increased by immobilization.

The combined action of immobilized β-amylase and pullulanase for the hydrolysis of starch has been reported[133]. β-Amylase degrades the outer chains while pullulnase splits the branch points, in effect opening the starch structure for each other.

Biomaterials that participate in synthesis reactions often require cofactors such as ATP, FMN and NADP. Before any synthesis reactions can begin to look economically attractive, regeneration of "used" cofactors must be achieved because of their high cost. For example, ATP and NADP retail in the US for $ 1,500 to 2,900 and $ 57000 per mole, respectively. Immobilized biomaterials can be expected to have a role in bringing down the cost of making these co-factors and that of their regeneration.

As has been shown[134, 135], an immobilized coenzyme system would have to yield greater than 1000 redox cycles to be of practical interest. A recent effort[136] in this respect on the immobilization of NADH using water soluble copolymers may be noteworthy. The researchers obtained 1000–2500 turnovers with their preparations from the epoxide-combining monomer 3-[4-(2,3-epoxypropoxy)butoxy]-2-hydroxypropyl acrylate and *N*-(methacrylyl)-2-glucosamine. Immobilized coenzymes and multienzymes have been reviewed recently[135, 137, 138].

Although the system was not considered to be feasible on an industrial scale, workers in Italy showed[139] that synthesis of L-alanine was feasible by co-entrapping two enzymes and a coenzyme in cellulose triacetate fibers. The two enzymes were lactic dehydrogenase (LDH) and alanine dehydrogenase (AlaDH). The coenzyme, which was recycled as shown below, was 4-($NAD^{\oplus}$-N^6)-3-hydroxybutyrylpolyethyleneimine ($NAD^{\oplus}$-Pol).

$$CH_3CHOHCOOH + NAD^{\oplus}\text{-Pol} \xrightarrow{LDH} CH_3COCOOH + NADH\text{-Pol} + H^{\oplus}$$

$$CH_3COCOOH + NADH\text{-Pol} + NH_4^{\oplus} \xrightarrow{AlaDH} CH_3CH(NH_2)COOH + NAD^{\oplus}\text{-Pol} + H_2O$$

$$CH_3CHOHCOOH + NH_3 \rightarrow CH_3CH(NH_2)COOH + H_2O$$

We may note that fermentation systems are conceptually the ultimate in co-immobilization. Many enzymes and coenzymes, inside the cell, combine their action to achieve cell growth or other metabolic action. Thus, the immobilization of cells themselves is a logical extension of multienzyme-coenzyme immobilization.

The growing worldwide recombinant DNA effort represents additional opportunities as well as competition for the immobilized biomaterial technology. Analytical and medical applications, not covered in this paper, should continue to evolve from this technology. The feasibility of using immobilized biomaterials to detoxify or transform toxic substances in blood has been established[140, 141].

In summary, immobilization offers the potential of economical exploitation of biomaterial activity. The development of immobilized biomaterial systems requires the involvement of biochemical, kinetic, and reactor design principles. The immobilized biomaterial technology has passed its early stages, as evidenced by worldwide commercial applications. Additional applications may be expected but perhaps at a slower pace.

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COMMUNICATIONS

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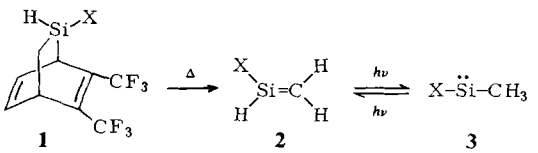
Reversible Photoisomerization between Silaethenes and Methylsilylenes (Methylsilanediyls)**

By *Hans Peter Reisenauer, Gerhard Mihm,* and *Günther Maier**

The energy hypersurface of $SiCH_4$ isomers is still the subject of intensive discussion[1]. In this connection the energetic relationship between silaethene and methylsilanediyl (methylsilylene)[***] plays a decisive role. Until now experimental results have been scarce[2], and only the photochemical formation of 1-methylsilaethene from dimethylsilanediyl at low temperature in the matrix has been demonstrated[2d]. We report for the first time the reversible photochemical conversion of silaethenes into methylsilanediyls.

The silaethenes **2a—2c** were generated by flash pyrolysis/matrix isolation from the precursors **1a—1c**, and isolated at 10 K in argon and nitrogen matrices[3]. Their characteristic spectroscopic data are shown in Table 1. The UV absorptions of the silaethenes completely disappear after being irradiated for a short period of time ($\lambda = 254$ nm, Hg low-pressure lamp); in contrast, the bands of the fragment (hexafluoro-*o*-xylene) remain unchanged. Simultaneously, new species are formed, which are characterized by a broad UV band shifted to long wavelength (intensity approximately 1/3 of the bands from **2a—2c**) with no structural features (Table 1). Similar changes occur in the IR spectra. In the case of **2a**, irradiation produces a marked shift of the Si—H stretching vibration to long wavelength. In the photoproducts from **2b** and **2c** a corresponding band is completely absent (Table 1).



1 **2** **3**

a, X = H; **b**, X = Cl; **c**, X = CH_3

Irradiation at the wavelength of the new UV absorptions (Hg high-pressure lamp with edge filters or monochromator) results in re-formation of silaethenes **2a—2c**. Subsequent short wavelength irradiation (254 nm) of these species again produces the above-mentioned isomerization. Forward and reverse reactions can be repeated several times. This revesibility of the photoconversion of **2** and the spectroscopic data suggest that the photoproducts are the methylsilanediyls **3a—3c**. The UV absorption of **3c** is identical with the value previously reported[2d]. The relatively low wavenumber of the Si—H stretching frequency

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[***] According to IUPAC Rule D-6.12, silylenes should be termed silandiyls.

in **3a** is also consistent with the methylsilanediyl structure. Hence, bands at approximately 2030 cm^{-1} are observed for SiH_2[7]. Calculations also indicate that the Si—H stretching frequency in methylsilanediyl lies approximately 200 cm^{-1} lower than in silaethene[8].

Table 1. IR and UV absorption bands of silaethenes **2a—2c** and methylsilanediyls **3a—3c** in argon and nitrogen matrices at 10 K.

	Silaethenes			Silanediyls	
	IR [cm^{-1}]	UV [nm]		IR [cm^{-1}]	UV [nm]
2a	Ar: 2239 (m), 2219 (m), 1350 (w), 985 (w), 927 (w), 817 (s), 741 (s)	258	**3a**	Ar: 2004 (m), 1935 (w)	480
	N_2: 2235 (m), 2214 (m), 1350 (w), 985 (w), 927 (w), 817 (s), 747 (s)	258		N_2: 1986 (w), 1978 (w), 1971 (m)	330
2b	Ar: 2230 (w), 984 (m), 843 (s), 699 (w), 544 (m), 537 (w)	255	**3b**	Ar: 1223 (m), 485 (m), 480 (w)	407
	N_2: 2230 (w), 980 (m), 840 (s)	255		N_2: 1220 (m)	387
2c	Ar: 2182 (m) [a], 1255 (w), 991 (m), 879 (m), 811 (m), 711 (w)	260 [2d]	**3c**	Ar: 840 (m)	460
				N_2: —	425

[a] Consistent with values in [2d].

The strong dependence of the position of the band of the Si—H stretching vibration in **3a** on the type of matrix is notable. Instead of the expected single band, two absorptions of different intensity at 2004 and 1935 cm^{-1} are found in an argon matrix. In a nitrogen matrix **3a** even exhibits three bands between 1970 and 1990 cm^{-1}. The influence of the matrix material is also reflected in the UV spectra of silanediyls: in the nitrogen matrix all the absorption maxima are hypsochromically shifted, in **3a** by as much as 150 nm.

Although the matrix effects mentioned still leave some questions open, the following conclusion, however, can be drawn: silaethenes and the isomeric methylsilanediyls are separately existing species, but can readily be interconverted *via* a photochemically induced 1,2-H shift.

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1a, 78167-41-6; **1b**, 83463-63-2; **1c**, 78715-28-3; **2a**, 51067-84-6; **2b**, 83463-64-3; **2c**, 38063-40-0; **3a**, 55544-30-4; **3b**, 77971-32-5; **3c**, 6376-86-9.

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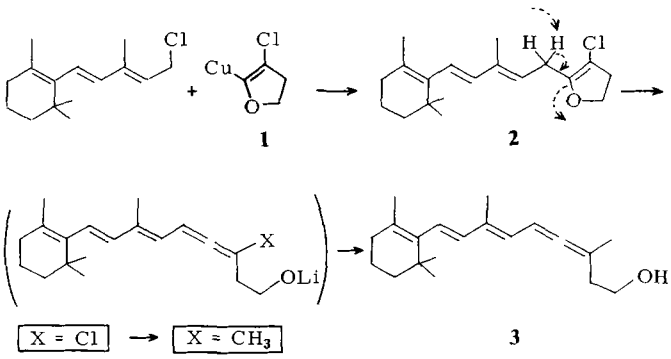
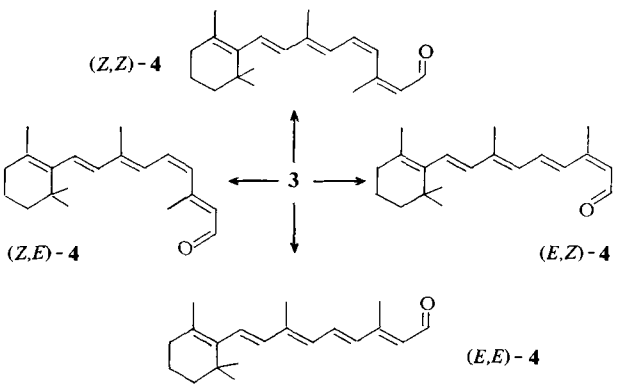
"Isoretinol" and Retinal: An Unorthodox, but Simple Entry to the Vitamin A Series

By *Renzo Ruzziconi* and *Manfred Schlosser**

Two equivalents of methyllithium react with 5-alkyl-4-chloro-2,3-dihydrofuran causing ring opening and substitution of the chlorine to give 3-methyl-3,4-dienols[1]. The chain of an alkyl halide (or alkyl toluenesulfonate) can be lengthened in this way by an unsaturated C_5-fragment which bears an OH-group and is branched at the appropriate position by a methyl group. Thus, a one-pot reaction using "2-β-ionylideneethyl chloride" as starting material leads *via* the dihydrofuran **2** to the "isoretinol" **3**[3] (55%). The key reagent is 3-chloro-4,5-dihydro-2-furylcopper **1**, accessible by treatment of the corresponding lithium compound[1] with copper(I) iodide.



The oxidation of **3** with dimethyl sulfoxide in presence of *N,N*-dicyclohexylcarbodiimide leads with concomitant double-bond shift to the four 11,13-stereoisomeric retinals (*Z,Z*)-, (*Z,E*)-, (*E,Z*)- and (*E,E*)-**4** (aldehyde proton: $\delta = 9.85$, 9.91, 10.13, and 10.01, respectively; ratio 1:1:4:5), which can be separated by liquid chromatography[7]. On addition of a trace of iodine the proportion of the *all-trans*-retinal (*E,E*)-**4** increases at the expense of the (*E,Z*)-isomer. The other two isomers disappear. In their place two new isomers are formed (each to the extent of *ca.* 10%) having (9*Z*,11*E*,13*Z*)- and (9*Z*,11*E*,13*E*)-configuration.



The wide applicability of the method was demonstrated by further natural product syntheses. Thus, 3,7,11-trime-

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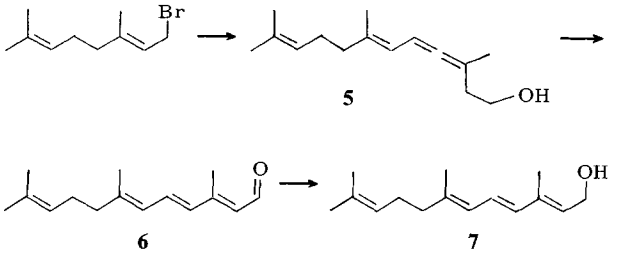
thyl-3,4,6,10-dodecatetraen-1-ol **5** was synthesized in 41% yield from geranyl bromide; **5** was then oxidized to the 4,5-dehydrofarnesal **6** (59%), which on reduction with $NaBH_4$ furnished the 4,5-dehydrofarnesol **7** (85%).



6 **7**

Most terpene syntheses are based on the coupling of appropriate isoprene building blocks. Only very seldom have other synthetic patterns, *e.g.* the condensation of a C_6-, C_{11}- or C_{16}-halide with (*Z*)-lithium-3-lithio-2-butoxide[11], been explored. The procedure now suggested here, namely separate incorporation of the linear C_4 moiety and the methyl group, has, *inter alia*, the advantage that the side chain can be varied within wide limits.

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CAS Registry numbers:
1, 83378-78-3; **2**, 83378-79-4; **3**, 74916-02-2; (9*Z*,11*E*,13*Z*)-**4**, 23790-80-9; (9*Z*,11*E*,13*E*)-**4**, 514-85-2; (9*E*,11*Z*,13*Z*)-**4**, 67711-05-1; (9*E*,11*Z*,13*E*)-**4**, 564-87-4; (9*E*,11*E*,13*Z*)-**4**, 472-86-6; (9*E*,11*E*,13*E*)-**4**, 116-31-4; **5**, 83378-80-7; (*Z*,*E*,*Z*)-**6**, 83378-80-8; (*E*,*E*,*Z*)-**6**, 74284-77-8; (*Z*,*Z*,*E*)-**6**, 83378-82-9; (*E*,*Z*,*E*)-**6**, 83378-83-0; (*Z*,*E*,*E*)-**6**, 83378-84-1; (*E*,*E*,*E*)-**6**, 64197-46-2; **7**, 67689-12-7; (*E*,*E*)-2-β-ionylideneethylchloride, 55732-70-2; geranyl bromide, 6138-90-5; (*E*)-4-chloro-5-(3,7-dimethyl-2,6-octadienyl)-2,3-dihydrofuran, 83378-85-2.

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[11] M. Schlosser, E. Hammer, *Helv. Chim. Acta 57* (1974) 2547.

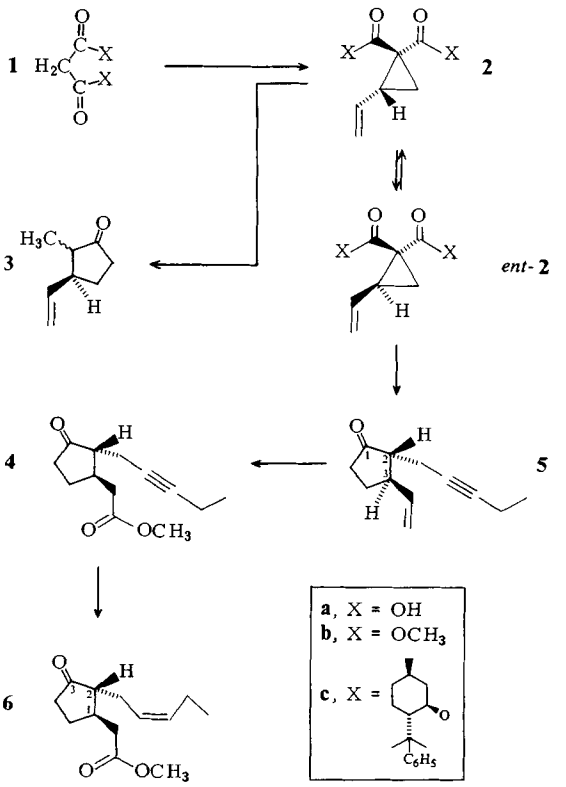
Asymmetric Synthesis of Methyl Jasmonate**

By *Gerhard Quinkert**, *Friedhelm Adam*, and *Gerd Dürner*

The cyclopropane derivative **2b** is a valuable synthetic building block: It has only one center of chirality, is readily available in an enantiomerically pure form[1], and for a total synthesis of 19-norsteroids has been transformed into ring D-building block **3** with complete inversion of configuration at the asymmetric center[2].

ent-**2b** is a potential building block for the synthesis of methyl jasmonate **6**[3], a valued perfumery ingredient. This enantiomer is, in principle, accessible by analogy to **2b**, *via* **2c**, with the latter obtained by an asymmetry inducing reaction of an (*E*)-1,4-dihalo-2-butene with **1c**[2], provided the alcohol component is not **1c**, but its enantiomer[6], which is only obtainable with difficulty.

However, a simpler route to *ent*-**2b** has now been found: refluxing a solution of **2c** in *p*-cymene leads to a separable



Scheme 1. **1c**→**2c**: $BrCH_2CH{=}CHCH_2Br$, $(C_8H_{17})_3(CH_3)NCl$, n-C_6H_{14}, NaOH, H_2O, 14 h, room temperature, 66.5%.—**2c**→*ent*-**2c**: *p*-cymene, 13 h, reflux, 57%.—*ent*-**2c**→*ent*-**2b**: C_2H_5OH, KOH, hydroquinone, reflux, 16 h; CH_2N_2, ether 72%.—*ent*-**2b**→**5**: $H_5C_2{-}C{\equiv}C{-}CH_2{-}CH(CO_2CH_3)_2$, CH_3OH, Na/CH_3OH, 10 min, 60 °C; removal of solvent; 1 h, 130 °C; CH_3OH, H_2O, 20 h, room temperature; 16 h reflux; conc. HCl; $NaH_2PO_4 \cdot 2H_2O$, 1 h, 0 °C; 4 h room temperature, 24%.—**5**→**4**: tetrahydrofuran, 9-borabicyclo[3.3.1]nonane, 2 h, room temperature; 30% H_2O_2, 3N NaOH; ether; Jones reagent, 14 h room temperature; CH_2N_2 65%.—**4**→**6**: petroleum ether, H_2/Lindlar catalyst, room temperature, 89%: chiroptical data for all the chiral compounds in Scheme 1 are shown in Table 2 of the Supplement.

equilibrium mixture (2.5 : 1) of the diastereomers **2c** and *ent*-**2c**. Hydrolysis of the latter, followed by esterification of the resulting dicarboxylic acid with diazomethane gives the desired compound *ent*-**2b**, which has been conventionally converted *via* **5** and **4**[8] into enantiomerically pure **6**. Previous syntheses of methyl jasmonate[9] have all led to mixtures of two racemates.

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

[1] The synthetic procedure affords enantiomerically pure **2b**; cf Fig. 3 in ref. [26].
[2] a) G. Quinkert, U. Schwartz, H. Stark, W.-D. Weber, H. Baier, F. Adam, G. Dürner, *Angew. Chem. 92* (1980) 1062; *Angew. Chem. Int. Ed. Engl. 19* (1980) 1029; b) G. Quinkert, U. Schwartz, H. Stark, W.-D. Weber, F. Adam, H. Baier, G. Frank, G. Dürner, *Liebigs Ann. Chem. 1982*, in press.
[3] Natural methyl jasmonate (E. Demole, E. Lederer, D. Mercier, *Helv. Chim. Acta 45* (1962) 685) consists of up to 90% of **6** and up to 10% of methyl [(*Z*,1*R*,2*S*)-3-oxo-2-(2-pentenyl)cyclopentyl]acetate (H. Gerlach, P. Kunzler, *Helv. Chim. Acta 61* (1978) 2503); correspondingly, racemic methyl jasmonate contains *rac*-**6** and 10% methyl [(*Z*,1*RS*,2*SR*)-3-oxo-2-(2-pentenyl)cyclopentyl] acetate.
[6] HX (E. J. Corey, H. E. Ensley, *J. Am. Chem. Soc. 97* (1975) 6908) and *ent*-HX (H. E. Ensley, C. A. Parnall, E. J. Corey, *J. Org. Chem. 43* (1978) 1610) can be obtained from (*R*)-pulegone.
[8] *rac*-**4** has been prepared and converted further by G. Büchi and B. Egger (*J. Org. Chem. 36* (1971) 2021).
[9] For syntheses of racemic methyl jasmonate see: R. V. Stevens, N. Hrib, *Tetrahedron Lett. 21* (1981) 4791.

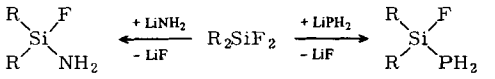
Synthesis of an *N*-Functionalized 1,3-Diaza- and a *P*-Functionalized 1,3-Diphospha-2,4-disilacyclobutane**

By *Uwe Klingebiel** and *Norbert Vater*

Reactions of dichlorodiorganosilanes with ammonia proceed with complete cleavage of hydrogen chloride to afford six- and eight-membered cyclosilazanes and higher condensation products[1]. Sterically demanding substituents lead to short-chain acyclic silazanes[2]. In this connection neither the formation of a four-membered ring $[R_2Si—NH]_2$ nor of an intermediate product $R_2SiCl—NH_2$ has been observed.

Cyclosilaphosphanes were obtained by reaction of dichlorodiorganosilanes with lithium phosphide or metalated organophosphanes[7]. The annelation can be attributed to the marked tendency of the initially formed unstable diphosphinosilanes to rearrange, although bis(*tert*-butylphosphino)dimethylsilane, $Me_2Si(PHtBu)_2$, has been isolated and after lithiation used in the synthesis of cyclosilaphosphanes[7].

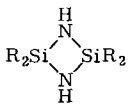
By allowing difluorodiorganosilanes to react with lithium amide or lithium phosphide, we obtained the surprisingly stable *N*-(fluorosilyl)amines **1** and **2**, and the *N*-(fluorosilyl)phosphane **3** (b.p. = 55 °C/18 torr, 38 °C/19 torr, and 70 °C/4 torr).



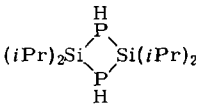
1, R = *t*Bu
2, R = *i*Pr

3, R = *i*Pr

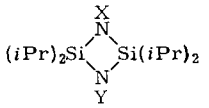
In an analogous fashion to the isoelectronic compound $(tBu)_2SiF(OH)$[9], **1** and **3** show no tendency to condense. **1**, **2** and **3** are readily *N*- and *P*-metalated by butyllithium, and in the absence of reactants form 1,3-diaza- (**7**, **8**) and 1,3-diphospha-2,4-disilacyclobutanes **9**, respectively (m.p. = 93 °C, b.p. = 55 °C/0.01 torr, and m.p. = 114 °C) upon cleavage of lithium fluoride.



7, R = *t*Bu; **8**, R = *i*Pr



9



10, X = Me_2FSi, Y = H
11, X = Y = Me_2FSi

Only one isomer was observed for **9** by NMR spectroscopy. The H atoms of the difunctional four-membered rings **7** and **8** can be mono- or dilithiated by C_4H_9Li, so that substitution reactions with elemental halides with retention of the ring framework are possible. For example, **8** forms *N*-mono- and *N,N'*-disubstituted products **10** and **11**, respectively (b.p. = 52 °C/0.01 torr, m.p. = 202 °C) with difluorodimethylsilane. All the novel compounds were characterized by NMR spectroscopy.

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CAS Registry numbers:
1, 83312-30-5; **2**, 83312-31-6; **3**, 83312-32-7; **7**, 83312-33-8; **8**, 83312-34-9; **9**, 83312-35-0; **10**, 83312-36-1; **11**, 83312-37-2;

[1] W. Fink, *Angew. Chem. 78* (1966) 803; *Angew. Chem. Int. Ed. Engl. 5* (1966) 760.
[2] L. H. Sommer, L. J. Tyler, *J. Am. Chem. Soc. 76* (1954) 1030.
[7] G. Fritz, R. Uhlmann, *Z. Anorg. Allg. Chem. 442* (1978) 95.
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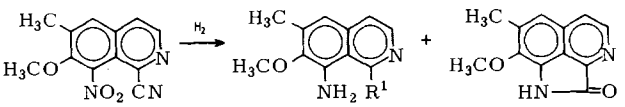
Catalytic Hydrogenation of 7-Methoxy-6-methyl-8-nitro-1-isoquinolinecarbonitrile to Unusual Products

By *Akinori Kubo**, *Naoki Saito*, *Shinsuke Nakahara*, and *Ryoichi Iwata*

There has recently been considerable interest in the crystal structures of 1,8-disubstituted naphthalenes with various nucleophilic groups ($N(CH_3)_2$, OH, OCH_3, NO_2) at one of the *peri*-positions and electrophilic groups (CO, CN) at the other, which exhibit intramolecular nucleophilic-electrophilic interactions[1]. However, few studies have been reported on the chemical properties of this class of compounds.

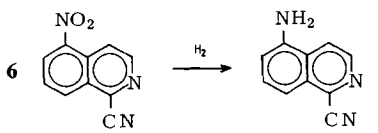
We now report the catalytic hydrogenation[2] of the title compound **1** in presence of 10% Pd/C (in anhydrous dimethylformamide (DMF), 3 h), which leads to formation of the novel heterocyclic lactam 8-methoxy-7-methylpyrrolo[2,3,4-*ij*]isoquinoline-2(1*H*)-one **4** (5.7%) in addition to the amines **2** (43%), **3** (13%)[3], and **5** (17%)[3]. Reduction of **1** in presence of PtO_2 (anhydrous DMF, 4 h) affords **2** (8.0%), **3** (22.0%), and trace amounts of **4** and **5**. Compound **4** was obtained in quantitative yield by treating **3** with conc. HCl (reflux, 30 min in ethanol).



1

2, R^1 = CN
3, R^1 = $CONH_2$
5, R^1 = H

4



6 **7**

The unexpected formation of lactam **4** can be rationalized by assuming that the oxygen atom of the nitro group of **1** is transferred to the carbon atom of the cyano group[2]. We, therefore, examined the catalytic hydrogenation of **2** and 5-nitro-1-isoquinolinecarbonitrile **6**. Under

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the same conditions as the reaction of **1**[2], **2** resisted hydrogenation and was recovered in 81% yield, whereas **6** furnished 5-amino-1-isoquinolinecarbonitrile **7** in 72% yield, but no amide.

These results provided additional evidence in support of the proposed mechanism. Finally, we note that the orientation of nitration of 7-methoxy-6-methylisoquinoline derivatives is determined unambiguously without correlation methods or spectroscopic analysis[5].

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[1] G. Procter, D. Britton, J. D. Dunitz, *Helv. Chim. Acta 64* (1981) 471, and references cited therein.

[2] **1** (259 mg, 1.06 mmol) was hydrogenated in 10 mL anhydrous DMF with 201 mg 10% Pd/C (3 h). The catalyst was filtered off and removal of the solvent gave 225 mg crude material, chromatography of which on 7 g silica gel (Kieselgel 60) afforded 97 mg (43.0%) **2**, m.p. = 137.5–138.5 °C (*n*-hexane). Elution with *n*-hexane/ethyl acetate (1 : 1), and *n*-hexane/ethyl acetate (1 : 1/1 : 2) gave 84 mg of the eluate, which after preparative thin layer chromatography on silica gel (CH_2Cl_2/acetone 1 : 1) yielded 31 mg (12.7%) **3**, m.p. = 104.5–106.0 °C (benzene) [3], 13 mg (5.7%) **4**, m.p. 262.5–264.0 °C (acetone) [3] and 34 mg (17.2%) **5**, m.p. = 78.0–79.0 °C (*n*-hexane).

[3] **3**: IR (KBr): 1560, 1630, 1658, 3340 cm^{-1}; UV (EtOH): $\lambda_{max} = 212$ nm ($\log\varepsilon = 4.59$), 252 (4.42), 323 (sh, 3.50), 365 (3.58); ^{1}H-NMR ($CDCl_3$): $\delta = 2.37$ (s, 3H), 3.75 (s, 3H), 5.60 (br s, 2H, D_2O exchangeable), 6.56 (br s, 1H, D_2O exchangeable), 6.95 (s, 1H), 7.43 (d, $J = 8$ Hz, 1H), 7.52 (br s, 1H, D_2O exchangeable), 8.13 (d, $J = 8$ Hz, 1H); MS: *m/z* 231 (M^+, 63%), 216 (54), 199 (100), 171 (57).—**4**: IR (KBr): 1490, 1590, 1635, 1690, 3190 cm^{-1}; UV (EtOH): $\lambda_{max} = 217$ nm ($\log\varepsilon = 4.39$), 259 (4.35), 345 (3.17), 392 (3.40); ^{1}H-NMR ([D_5]pyridine): $\delta = 2.37$ (s, 3H), 4.27 (s, 3H), 7.25 (s, 1H), 7.64 (d, $J = 8$ Hz, 1H), 8.92 (d, $J = 8$ Hz, 1H), 11.84 (s, 1H, D_2O exchangeable); MS: *m/z* 214 (M^+, 100%), 199 (63), 171 (56), 116 (15).

[4] H. Moll, H. Musso, H. Schröder, *Angew. Chem. 75* (1963) 295; *Angew. Chem. Int. Ed. Engl. 2* (1963) 212; H. Musso, H. Schröder, *Chem. Ber. 98* (1965) 1526.

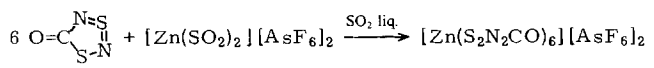
[5] S. F. Dyke in S. Coffey: *Rodd's Chemistry of Carbon Compounds*, 2nd ed., Elsevier, Amsterdam 1976, Vol. IV, Part F, Chapt. 27.

Synthesis and Structure of $[Zn(S_2N_2CO)_6][AsF_6]_2$—Sulfur-Nitrogen Rings as Ligands in Coordination Compounds**

By *Herbert W. Roesky**, *Manfred Thomas*, *Mathias Noltemeyer*, and *George M. Sheldrick*

Dedicated to Professor Rudolf Hoppe on the occasion of his 60th birthday

5-Oxo-1,3λ^4,2,4-dithiadiazole **1** can be prepared by reaction of $[(CH_3)_2SnN_2S_2]_2$ with carbonyl difluoride[1]. In order to clarify whether the coordination of the ligand to a metal atom takes place *via* oxygen, sulfur or nitrogen, we have investigated the reaction of **1** with the zinc complex **2** in liquid SO_2.



1 **2** **3**

After removal of SO_2, **3** precipitates as a colorless solid. **3** (m.p. 150 °C) is recrystallized from liquid SO_2; it is insoluble in CH_2Cl_2. Owing to their modest donor properties, the ligands **1** in **3** are very readily replaced by water molecules. In the IR spectrum of **3** the C=O stretching vibration is observed at 1560 cm^{-1}, *i.e.* it is shifted by 167 cm^{-1} to lower wave numbers compared to that of **1**. Thus, **1** should be coordinated to zinc *via* oxygen.

The X-ray structure determination shows that **3** crystallizes in the space group $P\bar{3}$ with $a = b = 1190.1(1)$, $c = 665.1(1)$ pm and $Z = 1$, $\rho_{calc} = 2.37$ Mgm^{-3}. The structure was solved by direct methods and refined to $R = 0.046$ and $R_w = 0.049$ for 1498 independent reflections with $F_0 > 3\sigma(F_0)$ and $Mo_{K\alpha}$-radiation.

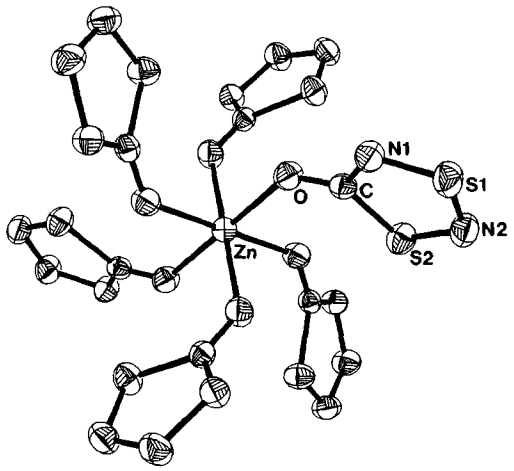


Fig. 1. Structure of $[Zn(S_2N_2CO)_6]^{2+}$, atom numbering and interatomic distances [pm], standard deviations in brackets: C—N(1) 134.7(3), N(1)—S(1) 157.6(3), S(1)—N(2) 157.0(3), N(2)—S(2) 161.7(2), S(2)—C 178.9(3), O—C 124.0(3).

In the $Zn(S_2N_2CO)_6^{2+}$ cation (Fig. 1) Zn is octahedrally coordinated: The maximum distortion from 90° is 1.4°. Zn lies on the special position with $\bar{3}$ symmetry and As on a threefold axis. The ligand **1**[2] is planar within experimental error, and possesses no crystallographic symmetry. The Zn—O—C angle is 134.2°. The C—O bond length in **3** (124.0(3) pm) is somewhat longer than in the free ligand (122.2(7) pm). The remaining bond lengths within the S_2N_2C ring show no significant change; the average S—N bond length in the uncoordinated ligand **1** is 159.5 and in **3** 158.8 pm.

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The complete manuscript of this communication appears in: *Angew. Chem. Suppl. 1982*, 1813–1818

CAS Registry numbers:
2, 83416-63-1; **3**, 83416-61-9.

[1] H. W. Roesky, H. Wiezer, *Angew. Chem. 87* (1975) 254; *Angew. Chem. Int. Ed. Engl. 14* (1975) 258.

[2] H. W. Roesky, E. Wehner, E. J. Zehnder, H. J. Deiseroth, A. Simon, *Chem. Ber. 111* (1978) 1670.

[*] Prof. Dr. H. W. Roesky, M. Thomas, Dr. M. Noltemeyer, Prof. G. M. Sheldrick
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$Tl(OtBu)_3Sn$: A Small Pentatomic Cage Molecule**

By *Michael Veith** and *Richard Rösler*

It is known that heavy main-group elements in low oxidation states can occur as essential constituents of cage

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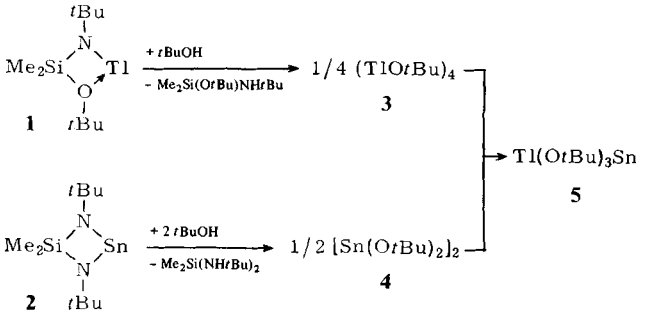
molecules. Hence, *e.g.* $TlOCH_3$[1] and *t*BuN=Sn[2] form tetramers, which consist of cubane-like Tl_4O_4 and Sn_4N_4 cages, respectively. In these compounds the main-group elements achieve a noble gas configuration through coordinative bonds.

We have now succeeded, for the first time, using Tl^I and Sn^{II}, in incorporating two low-valent elements from different main groups into a cage: for this purpose we made use of methods which we previously developed for the synthesis of Sn^{II} polycycles[2]. The pentatomic cage system **5** is obtained in high yield from the Tl^I and Sn^{II} molecular compounds **1**[3a] and **2**[3b] by allowing these to react with *tert*-butyl alcohol and subsequent reaction of the isolable intermediates of tetrameric **3**[4] and dimeric **4**.



5 is sublimable at 40 °C/0.001 torr, soluble in benzene, and displays only one signal ($\delta = 1.32$) in the ^{1}H-NMR spectrum, which indicates a highly symmetric molecule. The C_3 symmetry of the molecule is confirmed by X-ray structural analysis (Fig. 1). Tl and Sn are held together by three *t*BuO ligands, which results in a trigonal bipyramid: three oxygen atoms form the triangle, whereas the metal atoms are situated on the vertices.

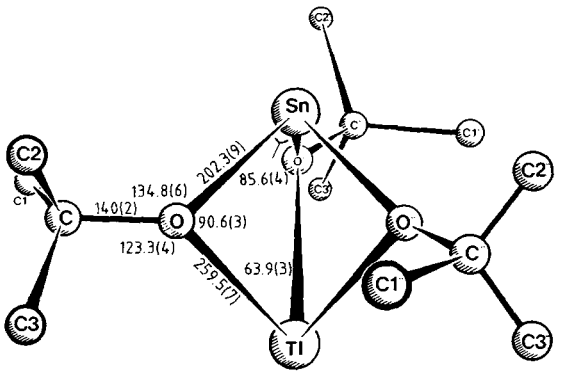
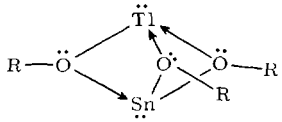


Fig. 1. Perspective representation of **5** with bond lengths [pm] and angles [°]. Crystal data: hexagonal, space group $P6_3/m$; $a = 994.4(5)$, $c = 1107(1)$ pm; $Z = 2$; $\rho_{exp} = 1.90$ g·cm^{-3}. 352 independent reflections, $R = 0.053$. Further details of the crystal structure investigation can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen, by quoting the following number CSD 50257, the name of the author, and the journal citation.

Due to the "encircling" the tin and thallium atoms come as close as 330.6(3) pm to each other. The relatively short SnO[2] and TlO distances[5] allow it to be presumed that an intramolecular ion pair, such as $Tl^{\oplus}[(OtBu)_3Sn]^{\ominus}$, is involved in **5**. This description, however, only corresponds to a mesomeric structure. The good solubility in benzene, ease of sublimation, and, above all, the crystal structure clearly indicate the nonpolar character of the molecule. In the crystal the molecules are arranged in a layer sequence AB, AB,..., in which a statistical defect along the hexagonal axis is observed (crystallographic point symmetry of **5**: C_{3h} (3/m)). The bonding behavior in the cage molecule **5** can be described thus:



According to the structural determination, the two-electron donor bonds are indistinguishable from the two electron single bonds.

Procedure

tert-Butyl alcohol (0.59 g, 0.008 mol resp. 1,2 g, 0.016 mol), is added dropwise to a solution of **1**[3a] (3.26 g, 0.008 mol) and **2**[3b] (2.58 g, 0.008 mol), respectively, in diethyl ether (20 mL) at −10 °C. Both solutions are stirred for 30 min and then combined. The reaction mixture is separated *in vacuo* whereby 3.9 g (90%) of colorless crystals of **5** sublime, which melt at 43 °C.

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1, 83437-07-4; **2**, 54724-62-8; **3**, 22520-89-4; **4**, 3275-19-2; **5**, 83437-08-5.

[1] L. F. Dahl, G. L. Davis, D. L. Wampler, R. West, *J. Inorg. Nucl. Chem. 24* (1962) 357.
[2] M. Veith, *J. Organomet. Chem. Libr. 12* (1981) 319.
[3] a) M. Veith, R. Rösler, *J. Organomet. Chem. 229* (1982) 131; b) M. Veith, *Angew. Chem. 87* (1975) 287; *Angew. Chem. Int. Ed. Engl. 14* (1975) 263.
[4] H. Schmidbaur, M. Bergfeld, F. Schindler, *Z. Anorg. Allg. Chem. 363* (1968) 73.
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New Dihydropyrans: Lewis Acid Catalyzed Cycloadditions of α,β-Unsaturated Acyl Cyanides to Simple, Unactivated Olefins and Dienes: A Readily Accessible Route to Derivatives of Rose Oxide**

By *Zeinhom M. Ismail* and *H. M. R. Hoffmann**

Cycloadditions of α,β-unsaturated carbonyl compounds to electron-rich olefins[1] are classified as Diels-Alder reactions with inverse electron-demand and furnish 3,4-dihydropyrans: Typically, enol ethers react with α,β-unsaturated aldehydes on heating in an autoclave at 160—180 °C (see *e.g.* formation of **3a** in Table 1). Previously, intermolecular cycloadditions of simple alkenes to α,β-unsaturated carbonyl compounds were unknown[2].

We have recently prepared a variety of α,β-unsaturated acyl cyanides[3] and now report that they can be activated by $AlCl_3$ to react with simple olefins at room temperature, giving novel dihydropyrans, *e.g.* **3b—3e**, in good yield. Even isobutene, **1e**, reacts with **2a** to give **3e** having two quaternary centers.

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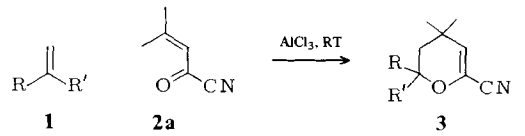


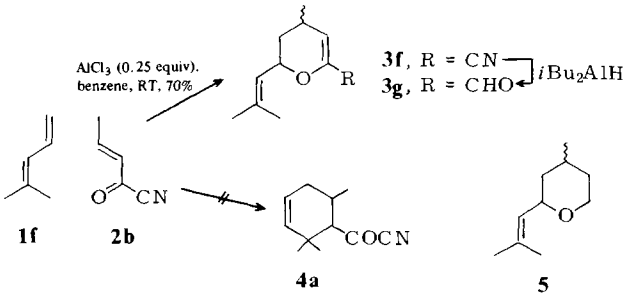
1 2a 3

Table 1. Dihydropyrans **3** from olefins **1** and 4-methyl-2-oxo-3-pentenenitrile **2a**.

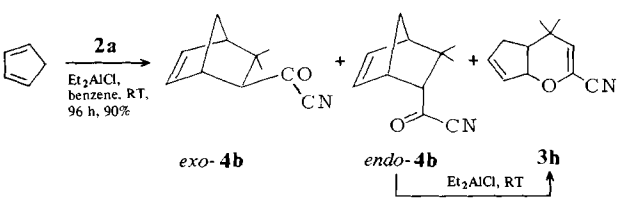
3	R	R'	$AlCl_3$: **2a**	Experimental conditions [a]	Yield [b] [%]
a	*i*PrO	H	—	160 °C, 10 h	76
b	Me_3SiCH_2	H	0.5	RT, 24 h	40
c	Ph	H	0.25	RT, 18 h	41
d	MeCH=CH	H	0.25	RT, 3 h	52 [c]
e	Me	Me	0.25	0—5 °C, 3 h	35

[a] For the preparation of **3a** neat reactants were used, otherwise reactions were conducted in benzene. [b] After Kugelrohr distillation. [c] 28% of the conventional Diels-Alder adduct is also formed.

Furthermore, 4-methyl-1,3-pentadiene **1f** and acyl cyanide **2b** furnish only **3f** in 70% yield (stereoisomeric ratio 59:41). Thus, a simple and convergent route has been opened to a variety of derivatives of rose oxide **5**[4], an important constituent of Bulgarian rose oil. The nitrile **3f** could also be converted into aldehyde **3g** in 70% yield.



Phenomenologically, the formation of these dihydropyrans can be regarded as a Diels-Alder reaction with inverse electron-demand, the LUMO of the heterodiene having been lowered by Lewis acid complexation. Mechanistically, Michael addition of the olefin to the activated α,β-unsaturated acyl cyanide, followed by formation of the second σ bond, must also be considered, especially when approach of the reacting termini is hindered (cf. **3e**).



With more reactive dienes, α,β-unsaturated acyl cyanides behave also as conventional dienophiles: from **2a** and cyclopentadiene **3h** is formed, in addition to *endo*-**4b** and *exo*-**4b**; *endo*-**4b** undergoes a facile Lewis acid catalyzed hetero-Cope rearrangement to give **3h** at room temperature.

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CAS Registry numbers:
1a, 926-65-8; **1b**, 762-72-1; **1c**, 100-42-5; **1d**, 504-60-9; **1e**, 115-11-7; **1f**, 926-56-7; **2a**, 38576-60-2; **2b**, 38576-57-7; **3a**, 83379-78-6; **3b**, 93379-79-7; **3c**, 83379-80-0; **3d**, 83379-81-1; **3e**, 83379-82-2; *cis*-**3f**, 83379-83-3; *trans*-**3f**, 83379-87-7; *cis*-**3g**, 83398-65-6; *trans*-**3g**, 83379-88-8; **3h**, 83379-84-4; *exo*-**4b**,

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$[Fe_3W_3S_{14}]^{4-}$, A Novel Hexanuclear, "Pure" Bimetal-Sulfur Cluster with $Fe_3(\mu_3\text{-}S)_2$ Center

By *Achim Müller**, *Winfried Hellmann*, *Hartmut Bögge*, *Rainer Jostes*, *Michael Römer*, and *Uwe Schimanski*

Dedicated to Professor Rudolf Hoppe on the occasion of his 60th birthday

Bimetal-sulfur clusters and complexes of Fe *and* Mo or W have generated extraordinary interest in relation to the active center of the MoFe protein of nitrogenase[1–4]; however, until now only a few different types of such compounds have been synthesized.

We have now succeeded in synthesizing the unusual bimetal cluster $[Fe_3W_3S_{14}]^{4-}$ **1** having a central $Fe_3(\mu_3\text{-}S)_2$ moiety, which displays remarkable structural details and is also interesting in relation to the recently discovered importance of Fe_3 centers in proteins[13]. **1** is formed from solutions of $[Fe(WS_4)_2]^{2-}$ **2**[1] and could be isolated in the crystalline state as $[(Ph_3P)_2N]_2(NEt_4)_2[Fe_3W_3S_{14}]$ **1a**, $(Ph_4P)(NEt_4)_3[Fe_3W_3S_{14}]$ **1b**, and $[(Ph_3P)_2N](NEt_4)_3[Fe_3W_3S_{14}]$ **1c** and characterized by elemental analysis, EH-SCCC-MO calculations, magnetic measurements, UV/VIS- [in CH_3CN: 630 (sh), 550 (sh), 465 (sh), 427, 365 nm], IR- [KBr pellet: 480 (st) (νWS_{term}), 443/435 (m) (νWS_{br}), 365 (w) ($\nu Fe\text{-}\mu_3\text{-}S$), 304 (m) cm^{-1} (νFeS)], resonance Raman-, and XPE-spectroscopy, as well as by complete X-ray structural analysis[**].

The three Fe atoms (Fe—Fe 272.1 pm) of the central unit form an equilateral triangle having a $\mu_3\text{-}S^{2-}$ ligand above and below this plane (Fe—S 229.4 pm). Each Fe atom is bidentately coordinated by a WS_4^{2-} ligand

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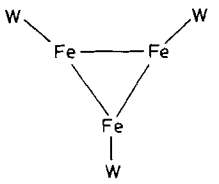
[**] Details of the crystal structure analysis can be obtained from the Fachinformationszentrum Energie—Physik—Mathematik, D-7514 Eggenstein-Leopoldshafen 2 by quoting the following number CSD 50287, the name of the author, and the complete citation of the journal.

(Fe—S_{br} 226.1, W—S_{br} 223.8, W—S_{term} 215.2, Fe—W 277.4 pm (average distances)). This results in a distorted tetrahedral environment for iron. The Fe_3W_3 moiety



is almost planar and exhibits metal-metal interactions[1] (the Fe atoms are strongly antiferromagnetically coupled). It is notable that the Fe_3S_2 cluster center is "held together" without the presence of doubly bridging ligands, which normally only occurs in electron-rich clusters with strong π-acceptors. This reconfirms the unusual properties of thiometalate ligands[1].

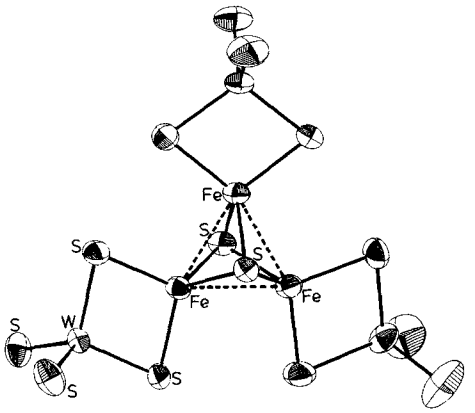


Fig. 1. Structure of the anion **1** (ORTEP plot) in crystals of **1b**. Space group $P\bar{1}$; $a = 1500.6(3)$, $b = 1475.4(3)$, $c = 1758.9(4)$ pm, $\alpha = 109.56(2)$, $\beta = 95.41(2)$, $\gamma = 106.10(2)°$; $Z = 2$; $R = 0.066$ for 8160 independent reflections ($F > 3.92\sigma(F)$); $Mo_{K\alpha}$ radiation.

It has recently been mentioned that apart from [2Fe-2S] and [4Fe-4S] moieties, Fe_3-sulfur cluster centers may also be widely distributed in proteins and enzymes[13]. For example, the 7Fe protein from *A. vinelandii*[13] not only contains a [4Fe-4S] but also a [3Fe-3S] cluster. Fe_3 groups perhaps occur *also in bimetal clusters* of proteins and enzymes (in nitrogenases *e.g.* a MoS_4 moiety could be considered to act as a bridging entity between two trinuclear clusters).

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CAS Registry numbers:
1a, 83399-09-1; **1b**, 83399-10-4; **1c**, 83416-28-8; **2**, 45845-01-0.

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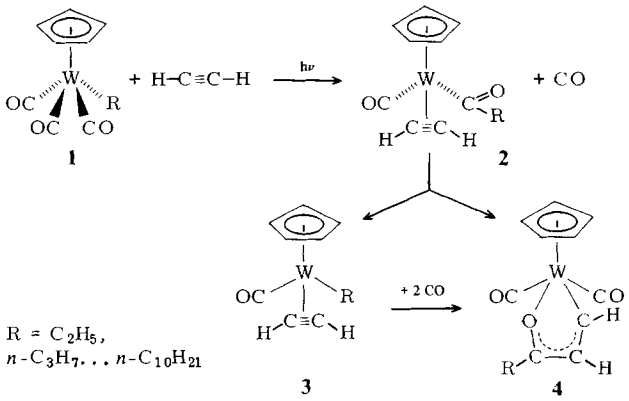
Novel Tungsten-Alkyl and Tungsten-Acyl Complexes with Acetylene as Four-Electron Ligand**

By *Helmut G. Alt**, *Manfred E. Eichner*, and *Brigitte M. Jansen*

Solutions of the alkyl complexes **1** are photochemically dealkylated by a rapid β-elimination[1]. The β-elimination also dominates over the photoinduced substitution of CO ligands when the complexes **1** are allowed to react with olefins or *n*-donors in solution. We have now observed that the reaction of **1** in pentane with acetylene leads to acetylene-acyl derivatives of the type **2**, photolytically generated carbon monoxide being inserted into the metal-alkyl σ-bond (cf. [4]). The complexes **2** can be smoothly converted in boiling toluene (110 °C, 4 min; without irradiation) into the CO-deficient compounds **3** and the CO-rich metallacycles **4**, which can be separated by column chromatography.

The alkyne complexes **2** and **3** are red, and, as expected, in the IR spectrum show one band for the terminal CO ligand, but no C≡C stretching vibrations in the region 2000—1500 cm^{-1}. In the ^{1}H-NMR spectrum the acetylene hydrogen atoms are strongly deshielded, and in the ^{13}C-NMR spectrum the acetylene carbon atoms are strongly deshielded; according to the mass spectra both types of complex are monomeric [*e.g.* **3**, $R = C_2H_5$: IR (pentane): $\nu(CO) = 1925$ cm^{-1}; ^{1}H-NMR ([D$_6$]acetone): $\delta = 5.48$ (s, 5), 12.44 (d, 1), 11.83 (d, 1) [J(H,H) = 1.2 Hz], 1.22 (m, 3), 0.96 (m, 1), 0.15 (m, 1); ^{13}C-NMR ([D$_6$]acetone): $\delta = 92.7$ (C_5H_5), 241.2 (CO), 191.3/185.7 (C_2H_5) [J(W,C) = 17.6 and 68.4 Hz], 26.6 (CH_3), 1.1 (W—CH_2) [J(W,C) = 94.7 Hz]; MS: $m/z = 332$ (M^+) referred to ^{184}W].



In acetylene complexes, in which the alkyne ligand clearly functions as a two-electron ligand, *e.g.* in $CpCr(CO)(C_2H_2)NO$[5], the corresponding C_2H_2 resonance signals in the ^{1}H-NMR ($\delta = 7.17/6.17$) and ^{13}C-NMR spectrum ($\delta = 89.8/75.8$; [D$_6$]acetone) appear far upfield. Such strongly deshielded alkyne resonance signals are also considered by other authors as an indication of the presence of alkynic four-electron ligands[6]. The unusually high rotation barrier around the tungsten-alkyne bond axis [*e.g.* **3**, $R = C_2H_5$: $\Delta G^{\neq} = 78.7$ (±4) kJ/mol] and the absence of a ν(C≡C) band in the IR spectrum about 1700 cm^{-1} also support this assumption. Extended Hückel calculations[8]

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on the model compounds $(C_5H_5)_2MoC_2H_2$, $Mo(CNH)_2(SH)_2(C_2H_2)$ and Mo(porphyrin)C_2H_2 confirm that both π-systems of the acetylene in **2** and **3** can interact with hybrid orbitals of the metal, so that the acetylene is to be regarded as a bidentate "biscarbene" ligand.

The complexes **3** are exceptionally stable towards UV light: **3**, R = *n*-C_3H_7, is changed to the extent of only 25% on irradiation ($\lambda > 300$ nm, 450 W) for one hour, when, according to the IR and ^{1}H-NMR spectra, the complex of type **2** is formed. This photochemical resistance of **3** further supports the assumption that the alkyne in **3** functions as a four-electron ligand, since otherwise β-elimination (in a 16-electron system) would be strongly favored as a result of the free coordination site on the metal, and would take place very rapidly.

The pentamethyl-substituted derivatives $C_5Me_5W(CO)_3R$ react analogously to complexes **1**; the products, however, are thermally more stable and crystallize better than **2**, **3**, and **4**. Substituted alkynes can also be employed instead of acetylene.

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CAS Registry numbers:
1 (R = C_2H_5), 51232-59-8; **2** (R = C_2H_5), 83436-95-7; **3** (R = C_2H_5), 83436-96-8; **3** (R = *n*-C_3H_7), 83447-49-8; **4** (R = C_2H_5), 83436-97-9.

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Preparation of Butatrienylamines from Butenynylamines

By *Lambert Brandsma**, *Peter E. van Rijn*, *Hermann D. Verkruijsse*, and *Paul von R. Schleyer*

Although the butatrienylamines (cumulenamines) **3** must occur as intermediates in the base-catalyzed rearrangement of the 3-buten-1-ynylamines (enynamines) **1** into the isomers **4**, all attempts to detect **3** have so far failed[1].

The isomerization **3** → **4** with potassium *tert*-butoxide in dimethyl sulfoxide or with potassium amide in liquid ammonia obviously proceeds much more rapidly than the formation of **3**. With a stronger base it should be possible to deprotonate **1** to **2** and to protonate **2** under kinetically controlled conditions to **3**. We report here on the isolation of the first butatrienylamine of type **3** (Table 1).

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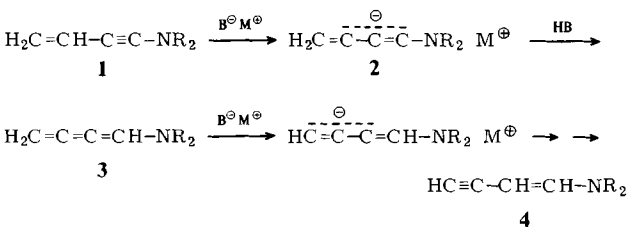

Table 1. Preparation of butatrienylamines **3** from butenynylamines **1**.

	2 R	B.p. [°C/torr]	n_D^{20}	Yield [%]	Contamination *trans*-**4** [%]
3a [a]	$2CH_3$	30/0.03 (70/10)	1.640	78	4
3b	$2C_2H_5$	45/0.03	1.598	66	3
3c	$2(CH_3)_2CH$	—	1.549	89	9
3d	$-(CH_2)_5-$	—	1.609	86	9
3e	$-(CH_2)_4O-$	—	1.613	82	8

[a] Spectral data of **3a** (representative for **3b**–**e**): ^{1}H-NMR (CCl_4, 20% solution TMS int.): $\delta = 2.73$ (CH_3, s), 3.90 (CH_2, m), 6.18 (CH, t, $^5J = 6.3$ Hz); ^{13}C-NMR (C_6D_6, TMS int): $\delta = 122.8$ (C1), 127.6 (C2), 162.2 (C3), 67.3 (C4), 40.0 (CH_3); IR (without solvent): 2065 s (C=C=C=C), 1635 s cm^{-1} (C=C).

Deprotonation of the readily accessible 3-buten-1-ynylamines **1**[2,3] with *n*-BuLi/*t*BuOK (1 : 1)[4] in hexane/tetrahydrofuran (THF) at low temperatures and protonation of the resulting species **2** (M = K) with *t*BuOH afforded butatrienylamines **3**. On work-up in the absence of water, **3a** and **3b** could be isolated[5]. In case of the higher boiling derivatives **3c**–**e** this methodology led to *cis*- and *trans*-**4** and to polymers. Very rapid aqueous work-up (water catalyzes the conversion **3** → *trans*-**4**), however, enabled the isolation of crude **3c**–**e**[5].

The butatrienylamines **3** are yellow liquids which rapidly turn brown at room temperature and form viscous polymers; the polymerization is catalyzed by oxygen. The refractive index is remarkably high: n_D^{20} for **3a** (96% pure) is 1.640; for comparison **1a**: 1.493, **4a**: 1.523[1].

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1a, 72530-40-6; **1b**, 15431-04-6; **1c**, 72530-41-7; **1d**, 83363-91-1; **1e**, 83363-92-2; **3a**, 83363-93-3; **3b**, 83363-94-4; **3c**, 83363-95-5; **3d**, 83363-96-6; **3e**, 83363-97-7.

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[4] M. Schlosser: *Polare Organometalle*, Springer, Berlin 1981.
[5] **3a**–**e**: A solution of **1** [1, 2] (0.05 mol) in THF (30 mL) was cooled to −100 °C, treated with 0.08 mol *n*BuLi in 56 mL hexane within 2–3 min, and then with 0.08 mol *t*BuOK in 20 mL THF within 1 min at −100 to −90 °C. After 5 minutes' vigorous stirring at −90 °C a solution of *t*BuOH (0.18 mol) in diethyl ether (30 mL) was added to the reaction mixture by means of a syringe. Subsequently, the temperature was raised to −25 °C. In the case of R = CH_3, 50 mL of paraffin oil and a few porcelain chips were also added to the mixture. After recondensation of the solvent at *ca.* 10 torr (bath temperature *ca.* 35 °C) into a flask cooled to −70 °C, **3a** was condensed together with a little *t*BuOH at 0.01–0.6 torr into a flask cooled to −60 °C. Renewed recondensation yielded **3a** (purity ≥ 96%).—In the other cases, after protonation with *t*BuOH the solvent was first removed at *ca.* 10 torr and the product recondensed at −70 °C. The residue was vigorously shaken with 120 mL pentane and the resultant suspension rapidly filtered through a G2 glass frit.—In the case of **3b**, 40 mL of paraffin oil was then added to the filtrate, pentane removed at *ca.* 20 torr, and the remaining paraffin oil-emulsion heated in a high vacuum. **3b** (97% pure) was isolated in the same way as **3a**. **3c**–**e** were obtained as crude products (purity 90–92%) after shaking the pentane solution

(−20 °C) for 30 s with 150 mL of an aqueous solution of 20 g K_2CO_3 cooled to 0 °C and subsequent drying over K_2CO_3, filtration, and evaporation of the solution to dryness at *ca.* 10 torr. The last traces of solvent and *t*BuOH were removed in a high vacuum (bath temperature <30 °C). Attempts to distill the compounds resulted in polymerization.

Tris(trimethylplumbyl)heptaphosphanortricyclene $P_7(PbMe_3)_3$[1]

By *Dieter Weber, Carlos Mujica,* and *Hans Georg von Schnering**

Molecular compounds containing phosphorus-lead bonds are still a rarity. The few known examples include the substituted phosphanes $P(PbR_3)_3$ and $R—P(PbR_3)_2$ described by *Schumann et al.*[2]. Entry to these P—Pb systems, however, is essentially thwarted by the lability of the P—Pb bond. It is well known that no binary lead phosphides exist, and that molten lead is even used for the crystallization of Hittorf's phosphorus. As regards ternary compounds, the only known examples are the polyphosphides of the type $HgPbP_{14}$ discovered by *Krebs et al.*[5]. We have now been able to prepare $P_7(PbMe_3)_3$ **3** from $P_7(SiMe_3)_3$ **1**[6] and $ClPbMe_3$ in a facile reaction. The reaction proceeds (presumably according to an S_N2 mechanism) practically quantitatively in monoglyme at −50 °C with cleavage of $ClSiMe_3$. In complete contrast to the very sensitive Si-compound **1**, the colorless crystals of the Pb-compound **3** can be stored for days in air without any notable change, until finally decomposition with darkening in color (precipitation of lead) takes place. The analogous Sn-compound $P_7(SnMe_3)_3$ **2** can be obtained in the same way by reaction with $ClSnMe_3$[7]. Finally, the analogous Ge-compound can also be synthesized, directly, in a heterogeneous reaction from Na_3P_7 and $ClGeMe_3$.

Mass spectroscopically, only fragment ions are detectable above 298 K, a clear indication of the thermal lability of the P—Pb bond. Thus, it is understandable that **3**, unlike **1**, cannot be sublimed. The formation of **3** is favored by its relatively sparing solubility and by the volatility of $ClSiMe_3$. The IR spectra of all four $P_7(MMe_3)_3$ compounds with M = Si, Ge, Sn, Pb are characterized on the one hand by the intense M—C vibrations, dependent upon the atomic weight, and on the other by two groups of almost invariant skeletal vibrations of the central nortricyclene system.

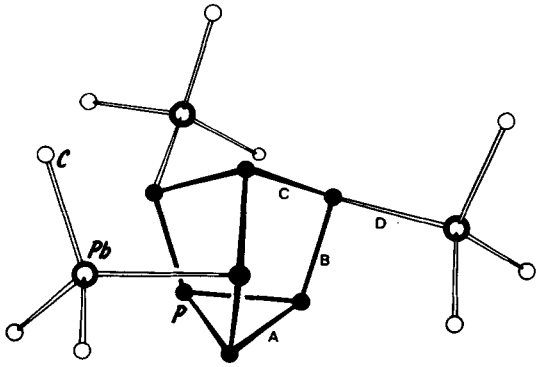

Fig. 2/3. Structure of $P_7(PbMe_3)_3$ **3**. Average bond lengths: A = 221.2, B = 217.6, C = 217.8, D = 261.1 pm ($\bar{d}$(Pb—C) = 219 pm). Crystal structure: $P2_1$ (No. 14); a = 990.8(2), b = 1819.1(3), c = 697.0(1) pm; β = 99.66(2)°; Z = 2; 2348 *hkl*; $Mo_{K\alpha}$ radiation; R = 0.052.

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The X-ray structure analysis (Fig. 2/3) reveals **3** as being isotypic with **1**[10]. The bond lengths d(P—Pb) average 261.1 pm ($\Sigma R_{cov.}$ = 258 pm). The bond lengths and angles in the nortricyclene framework closely resemble those in the other compounds[10]. The twisting of the P-skeleton about the threefold axis in **1**, determined by the steric interaction of the substituents with the free electron pairs on the bridge atoms, is also observed once again. The $P_7(MMe_3)_3$ molecules are chiral; in each case only one enantiomer is present in the crystal ($P2_1$). In the case of the Pb compound we were able to determine the absolute configuration. Since the crystals are relatively easy to handle there is the possibility of being able to separate the enantiomers.

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3, 83417-29-2.

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Control of the Conformation of Transition States in Intramolecular Diels-Alder Reactions with Inverse Electron Demand**

By *Lutz-F. Tietze**, *Hartmut Stegelmeier, Klaus Harms,* and *Thomas Brumby*

In memoriam, Otto Bayer

Intramolecular Diels-Alder reactions permit the stereocontrolled synthesis of several chiral centers in one step[1a]; in this connection the configuration of at least two of the newly formed chiral centers is determined by the conformation of the chain linking the reacting π systems. We were able to demonstrate that 2-alkylidene-1,3-dicarbonyl compounds of type **1** lead exclusively, within a few minutes at 20 °C, to *trans*-annelated products **2** *via* an intramolecular Diels-Alder reaction with inverse electron demand[1b]. The chiral center in the chain of this system enables a stereoinduction with *de*-value >98% to be achieved[2].

Exclusively *cis*-annelated products are formed from arylidene compounds of type **3**, in which two C atoms are part of an aromatic ring. In this case the *endo*-transition state **3B** is energetically more favorable than the *exo*-transition state **3A**[3a]. The 2-benzylidene-1,3-dicarbonyl compounds **3** can be obtained by condensation of aldehydes **4** with 1,3-dicarbonyl compounds, *e.g.* **5** or **7**, in presence of

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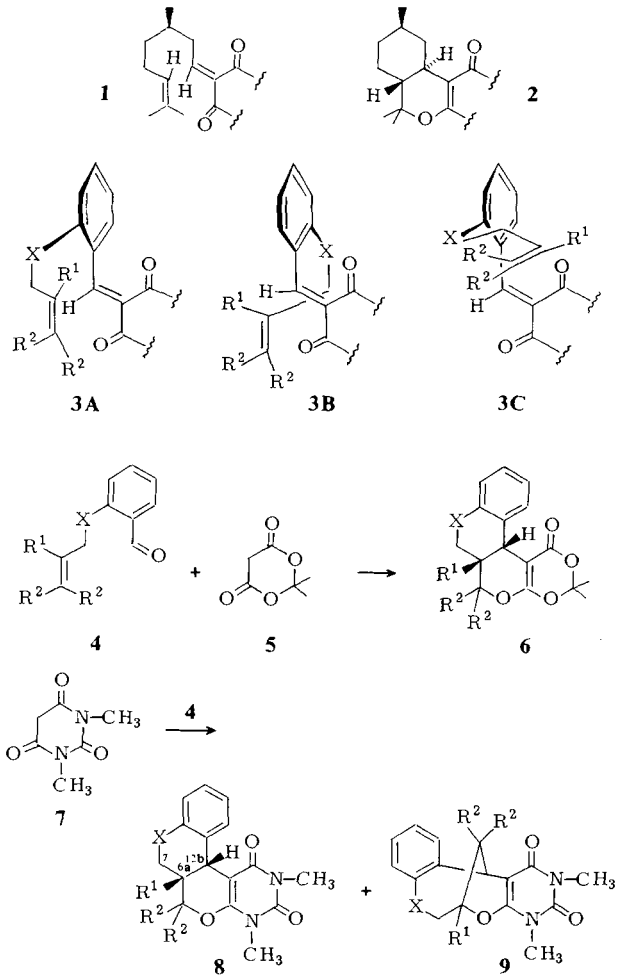

Scheme 1. **3-9**: **a**, X = CH_2, R^1 = H, R^2 = CH_3; **b**, X = O, R^1 = H, R^2 = CH_3; **c**, X = N–Ms, R^1 = H, R^2 = CH_3; **d**, X = S, R^1 = H, R^2 = CH_3; **e**, X = O, R^1 = R^2 = H; **f**, X = O, R^1 = CH_3, R^2 = H

Table 1. Yields and melting points of the cycloadducts from **4a**—**4f** and **5** or **7**.

Educt	Cycloadduct	Yield [%]	M.p. [°C]
4a + **5**	**6a**	65	105 (decomp.)
4a + **7**	**8a**	69	225
4b + **5**	**6b**	73	131 (decomp.)
4b + **7**	**8b**	91	206
4c + **7**	**8c**	53	250
4d + **7**	**8d**	33 (65) [4]	253
4e + **7**	**8e** + **9e**	70; 4	184; 186
4f + **7**	**9f**	81	174

catalytic amounts of ethylenediammoniumdiacetate in CH_2Cl_2 or CH_3CN. They can only be isolated, however, in the case of the reaction of **4e** and **4f** with **5** or **7** (yield >90%). **4a** and **4b** react with **5**, and **4a**—**4d** with **7** (Table 1) within 5 h at 20 °C *via* intermediate arylidene compounds[4], which can be detected by ^{1}H-NMR spectroscopy (H—C≡C—CO: $\delta \approx 8.8$), to afford cycloadducts **6a**—**6b** and **8a**—**8d**, respectively[5a].

The presence of a heteroatom (X = O, N—Ms, S) instead of a CH_2 group in the chain adjacent to the aryl moiety has no product determining influence on the conformation of the transition state. This was expected for **3b** and **3c**, since substitution of a CH_2 group in carbocycles by an oxygen or a nitrogen atom causes only a slight conformational change. The substituents on the dienophile have considerable influence on the reaction rate and the type of transition state. Thus, **3e** (from **4e** and **7**) and **3f** (from **4f** and **7**) react first at 135 °C (12 h, xylene). A mixture of the annelated product **8e** and the bridged product **9e** (20:1) is obtained from **3e**, and, exclusively, the bridged product **9f** from **3f**; this selectivity is surprising, but is qualitatively consistent with the results expected from the HOMO coefficients of the dienophile. The bridged compounds are presumably formed from conformation **3C**[3b].

The conformation of the 2-benzylidene-1,3-dicarbonyl compounds **3** (from **4e** and **4f**, and **5** or **7**) in the crystal[5b], which are stable at 20 °C, however, precludes a Diels-Alder reaction in the solid state.

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[3] a) The (*E*)-heterodiene moiety in **3** is assumed to be the reacting system involved in the formation of the annelated products **6** and **8**. However, reaction of the (*Z*)-heterodiene moiety *via* an *exo*-transition state would yield the same products. But it has been shown that (*Z*)-heterodienes react sluggishly in intermolecular Diels-Alder reactions: G. Desimoni, G. Colombo, P. P. Righetti, G. Tacconi, *Tetrahedron 29* (1973) 2635; cf. also B. B. Snider, J. V. Duncia, *J. Org. Chem. 45* (1980) 3461. b) It must be assumed that either the (*Z*)-heterodiene moiety in **3** or a two-step mechanism is involved in the formation of the bridged products **9**, since otherwise a highly strained transition state would result.

[4] When the reaction of **4d** with **7** is quenched after 30 min and the mixture worked-up at low temperature, **3d** can also be isolated in 84% yield. **3d** forms the cycloadduct **8d** in boiling toluene (78% yield).

[5] a) **8b**: ^{1}H-NMR ($CDCl_3$): δ = 1.23 (s; 3H, CH_3), 1.63 (s; 3H, CH_3), 2.15 (dt, J = 6.0 Hz, J = 3.0 Hz; 1H, 6a-H), 3.35 (s; 3H, N—CH_3), 3.45 (s; 3H, N—CH_3), 4.35 (d, J = 6.0 Hz; 1H, 12b-H), 4.43 (*ABX*, J = 11.2 Hz, J = 3.0 Hz; 2H, 7-H_2), 6.75—7.50 (m; 4H, aromat. H); b) G. Sheldrick, K. Harms, L.-F. Tietze, unpublished results.

Erythro-Selective Aldol-Type Addition of Titanated Aldehyde-Hydrazones**

By *Manfred T. Reetz, Rainer Steinbach,* and *Kurt Kesseler**

In contrast to metal-enolates derived from ketones and esters the analogous reagents from aldehydes are not suitable for diastereoselective aldol-additions[1,2]. For example, lithium- and titanium-aldehyde-enolates exhibit practically no diastereoselectivity[3]. While lithiated aldehyde-hydrazones **2**[4] show no improvement (LDA = lithium diisopropylamide), their titanation with chlorotitanium triisopropoxide or bromotitanium tris(diethylamide) leads to the novel reagents **3**, which react *erythro*-selectively with aldehydes **4** to afford the adducts **5** and **6** (Table 1). Furthermore, the chemical conversion of **3** (X = isopropoxide) is higher than that of **2**. In the titanium series the alkoxides are generally markedly more efficient than the amides. The diastereomers **5** and **6** were isolated and separated by low-

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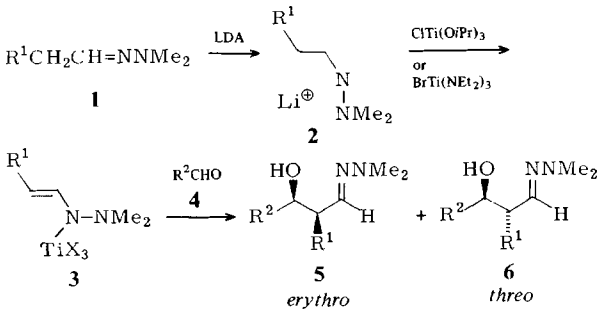
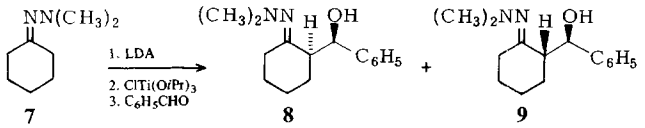


Table 1. *Erythro*-selective addition of titanium reagents **3** to aldehydes **4**.

R^1	X	R^2	Conversion [%]	5 : 6
CH_3	O*i*Pr	C_6H_5	**a** (80)	91 : 9
CH_3	NEt_2	C_6H_5	**a** (61)	85 : 15
C_6H_5	O*i*Pr	C_6H_5	**b** (95)	98 : 2
C_6H_5	O*i*Pr	*p*-$NO_2C_6H_4$	**c** (40)	98 : 2
C_6H_5	O*i*Pr	CH_3	**d** (95)	96 : 4
C_6H_5	NEt_2	CH_3	**d** (50)	≈90 : 10
C_6H_5	O*i*Pr	$CH(CH_3)_2$	**e** (78)	98 : 2
$(CH_3)_2CH$	O*i*Pr	C_6H_5	**f** (78)	94 : 6
CH_3	O*i*Pr	CH_3	**g** (61)	95 : 5
CH_3	O*i*Pr	$C(CH_3)_3$	**h** (70)	93 : 7

pressure liquid chromatography[1]. The product ratio was determined by analysis of the 400-MHz ^{1}H-NMR spectra.

The *erythro*-selectivity is also observed with titanated ketone-hydrazones (*e.g.* **7** → **8**), a finding which is to be compared with the *erythro*-selective behavior of titanium enolates from ketones[5].



> 98 : < 2

In the case of **3** ($R^1 = C_6H_5$, $X = N(C_2H_5)_2$) it was possible to record a ^{1}H-NMR spectrum which is in line with the *E*-configuration. The observed stereoselectivity is therefore surprising, because *E*-configurated ketone-enolates usually react *threo*-selectively[1,2]. In the case of a cyclic transition state, both chair and boat conformations are conceivable.

Aside from chlorotitanium triisopropoxide, titanium tetraisopropoxide can also be used for the titanation. However, in this case ate-complexes are formed which show less pronounced *erythro*-selectivity. Finally, titanated Schiff bases likewise behave *erythro*-selectively.

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1 ($R' = CH_3$), 7422-93-7; **1** ($R' = C_6H_5$), 65259-56-5; **1** ($R' = (CH_3)_2CH$), 13063-58-6; **3** ($R' = CH_3$, $X = OCH(CH_3)_2$), 83314-04-9; **3** ($R' = CH_3$, $X = N(C_2H_5)_2$), 83314-05-0; **3** ($R' = C_6H_5$, $X = OCH(CH_3)_2$), 83314-06-1; **3** ($R' = C_6H_5$, $X = N(C_2H_5)_2$), 83314-07-2; **3** ($R' = (CH_3)_2CH$, $X = OCH(CH_3)_2$), 83314-08-3; **4** ($R^2 = C_6H_5$), 100-52-7; **4** ($R^2 = p$-$NO_2C_6H_4$), 555-16-8; **4** ($R^2 = CH_3$), 75-07-0; **4** ($R^2 = CH(CH_3)_2$), 78-84-2; **4** ($R^2 = C(CH_3)_3$), 630-19-3; **5** ($R' = CH_3$, $R^2 = C_6H_5$), 83314-09-4; **5** ($R' = C_6H_5$, $R^2 = C_6H_5$), 83314-10-7; **5** ($R' = C_6H_5$, $R^2 = p$-$NO_2(C_6H_4)$, 83314-11-8; **5** ($R' = C_6H_5$, $R^2 = CH_3$), 83314-12-9; **5** ($R' = C_6H_5$, $R^2 = CH(CH_3)_2$, 83314-13-0; **5** ($R' = (CH_3)_2CH$, $R^2 = C_6H_5$), 83314-14-1; **5** (R', $R^2 = CH_3$), 83314-15-2; **5** ($R' = CH_3$, $R^2 = C(CH_3)_3$), 83314-16-3; **6** ($R' = CH_3$, $R^2 = C_6H_5$), 83314-17-4; **6** ($R' = C_6H_5$, $R^2 = CH_3$), 83314-18-5; **7**, 10424-93-8; **8**, 83314-19-6; **12**, 83314-20-9; *N*-propylidenecyclohexanamine, 1195-49-9; titanium tetraisopropoxide, 546-68-9; $Cl[TiOCH(CH_3)_2]_3$, 20717-86-6; $TiCl_4$, 7550-45-0; $BrTi(NEt_2)_3$, 24690-84-4.

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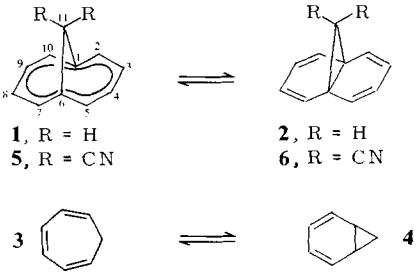
Theoretical Investigations on the Valence Tautomerism between 1,6-Methano[10]annulene and Tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene

By *Dieter Cremer** and *Bernhard Dick*

1,6-Methano[10]annulene **1** must, on the basis of its physical and chemical properties, be described as a Hückel aromatic system with a delocalized π-electron decet[1a-d]. Investigations on C-11-substituted 1,6-methano[10]annulenes, however, suggest that **1** can transform into the valence tautomer tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene **2** in solution[1c,d]. There is the possibility of a rapid reversible valence tautomerism of the type **1** ⇌ **2**, similarly to that assumed for the system cycloheptatriene **3** - norcaradiene **4**[1e-g].



1, R = H
5, R = CN

2, R = H
6, R = CN

According to experimental and theoretical estimates[2], **4** is destabilized by about 4–12 kcal/mol compared to **3**. Accordingly, the equilibrium **3** ⇌ **4** is shifted far over to the side of the cycloheptatriene. However, detection of the norcaradiene component has so far only been possible in an indirect way. Thus, **3** reacts like **1** with dienophiles to give Diels-Alder products, indicating a previous rearrangement **3** ⇌ **4** or **1** ⇌ **2**. However, it cannot be ruled out that the norcaradiene component is first formed at the moment of reactive collision with the dienophile[2a].

To clarify this problem we have determined the energy profile of the valence tautomeric processes **1** ⇌ **2** and **3** ⇌ **4**, respectively, by *ab initio* calculations and therefrom obtained the energy differences $\Delta E = E(2) - E(1)$ and $\Delta E = E(4) - E(3)$[3]. After taking into account vibration and entropy effects values of 4.5 and 5.6 kcal/mol, respectively, result for the difference in the free energies ΔG^0, which corresponds to concentrations of about 0.05% **2** and 0.01% **4** at room temperature.

The valence tautomerization of **1**, like that of **3**, is characterized by an asymmetric double-well potential (Fig. 1). According to our calculations, an asymmetric single-well potential, as has been discussed for the 11-cyano-11-methyl derivative[4a], can be ruled out for the rearrangement **1** → **2**. For the energy barriers ΔE^+ of the forward and reverse reactions, we find values of 7.3 and 2.3 kcal/mol, respectively. These values are about 3 kcal/mol smaller than the barriers calculated for the equilibrium **3** ⇌ **4**. Appar-

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ently formation of the cyclopropane bond is favored as a result of the shorter 1,6-distance in **1** (2.26 Å as opposed to 2.50 Å in **3**[3]), whereas in **2** the interaction of the Walsh orbitals of the three-membered ring with the π-orbitals of the butadiene moieties indicates the far better π-conjugation in **1**.

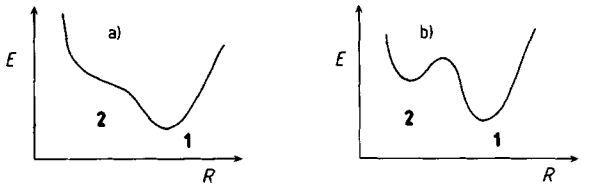

Fig. 1. Schematic representation a) of an asymmetric single-well potential and b) of an asymmetric double-well potential for the valence tautomeric equilibrium **1** ⇌ **2**. *R* is distance between C-1 and C-6.

According to experimental and theoretical investigations on cycloheptatrienes, substituents can shift the valence tautomeric equilibrium to the side of the norcaradiene[4b-e]. Thus, *Ciganek* synthesized 7,7-norcaradienedicarbonitrile as the first norcaradiene derivative in this way[4b].

The electronic influence of the two CN groups has been calculated to amount to about 10 kcal/mol[3] in the case of the cycloheptatriene. If this value is extended to the system **1** ⇌ **2**, then it can be predicted that tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene-11,11-dicarbonitrile **6** is more than 5 kcal/mol more stable than the valence tautomeric 1,6-methano[10]annulene-11,11-dicarbonitrile **5**. This prediction is confirmed by the synthesis of **6** and its spectroscopic and structural chemical characterization carried out by *Vogel et al.*[5].

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[3] The equilibrium geometries of **1** to **4** were determined by means of the MNDO method and by Hartree-Fock (HF) calculations with minimal basis (STO-3G). The potential curve for the transformation **1** ⇌ **2** was determined by HF/4-31G calculations. The absolute energies for **1** and **2** are −421.67075 and −421.66278 Hartree, respectively. In the case of **3** and **4** additional HF/6-31G* calculations were carried out [*E*(**3**) = −269.68035, *E*(**4**) = −269.67128 Hartree]. Correlation effects were estimated according to the Møller-Plesset perturbation method (2nd order). Finally, the zero point vibration energies as well as vibration contributions to enthalpy and entropy have been determined by force field calculations (D. Cremer, B. Dick, D. Christen, unpublished results).

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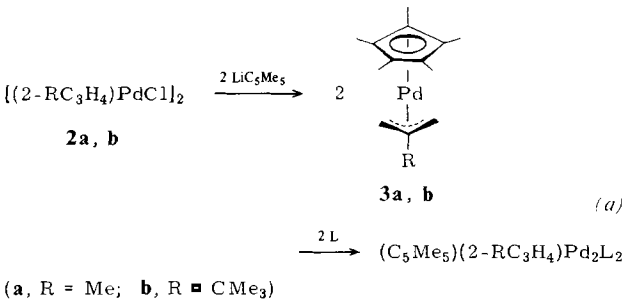
Synthesis of Pd(η²-CH₂=C₅Me₄)L₂: Formation of a Fulvene Ligand by Metal-Assisted H-Shift from Pentamethylcyclopentadienyl**

By *Hans-Jürgen Kraus* and *Helmut Werner**

Dedicated to Professor Rudolf Hoppe on the occasion of his 60th birthday

In connection with our studies on the chemistry of dinuclear palladium complexes of the type $(C_5H_5)(2\text{-}RC_3H_4)Pd_2L_2$ (**1**)[10] we attempted the preparation of the corresponding pentamethylcyclopentadienyl compounds *via* reaction sequence *(a)*. We expected these compounds to exhibit greater kinetic stability than the C_5H_5 complexes **1** regarding cleavage of the C_5Me_5—Pd_2 bond[12].



The reaction of **2a** or **2b** with LiC_5Me_5 in pentane (25 °C, 2 h) leads to **3a** and **3b**, respectively (*ca.* 85% yield, red crystals, m.p. 15—17 °C and 58 °C, respectively, correct elemental analysis, ^{1}H-NMR and mass spectra).

3b does not react with $P(iPr)_3$ or PPh_3, even on prolonged heating at 50—60 °C. Reaction with PMe_2Ph and $PMePh_2$ leads to cleavage of both the C_5Me_5—Pd as well as the allyl-Pd bond, with formation of the known palladium(0) compounds $Pd(PR_3)_4$. In contrast, the reactions with PMe_3 and $P(OMe)_3$ in toluene (50—60 °C, 5 h) afford the 1,2,3,4-tetramethylfulvene complexes **4** and **5** in 80—90% yield as bright yellow, air-sensitive solids which are readily soluble in all the common solvents and can be stored almost indefinitely at −30 °C under nitrogen.

The room-temperature ^{1}H-NMR spectra of **4** and **5** (in C_6D_6) indicate that the compounds have a fluxional structure in solution. Considerably broadened singlets are observed both for the protons of the exocyclic CH_2-groups as well as for the methyl protons of the ring. Signal sharpening occurs (in $(CD_3)_2CO$), and on cooling at −10 °C (**4**) and −25 °C (**5**), respectively, the splitting pattern to be expected for the constitution given in Scheme 1 is observed. From the large upfield shift of the signal of the C=CH_2 protons of $\delta = 5.47$ in the free tetramethylfulvene to $\delta = 2.54$ and 3.04 in **4** and **5**, respectively, the large PH-coupling constants, and the observation of two (and not of four) signals for the C—CH_3 groups, it can be concluded that the PdL_2 moiety is coordinated to the exocyclic C=C double bond. The palladium atom should lie in a plane with the two phosphorus atoms and the carbon atoms of the C=CH_2 bond. The platinum compounds $Pt(\eta^2\text{-}CH_2{=}C_5Ph_4)L_2$ (L = PPh_3, $PMePh_2$, PMe_2Ph, $AsPh_3$,

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[**] Investigations on the Reactivity of Metal-π-Complexes, Part 38. This work constitutes part of the Dissertation by H.-J. Kraus, Universität Würzburg 1981.—Part 37: [12].

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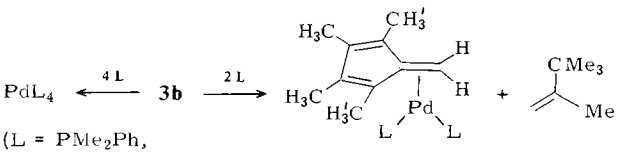

(L = PMe_2Ph, $PMePh_2$)

4, L = PMe_3
5, L = $P(OMe)_3$

Scheme 1

CN*t*Bu) recently described by *Stone et al.*, which are formed from $Pt(\eta^2\text{-}CH_2{=}C_5Ph_4)C_8H_{12}$ and L, have an analogous structure[14].

The ^{13}C-NMR data are also consistent with the structure proposed for **4** and **5**. The signals of the carbon atoms of the $C{=}CH_2$ bond are each split into a doublet of doublets by coupling with two different ^{31}P-nuclei, and the signal of C^6 shows an additional triplet splitting in the off-resonance spectrum, due to CH coupling. The non-equivalence of the phosphane and phosphite ligands, respectively, is revealed in the ^{31}P-NMR spectrum by two doublets [**4**: $\delta = -21.47, -23.79$; $J(PP) = 28.3$ Hz. **5**: $\delta = 155.0, 152.34$; $J(PP) = 25.3$ Hz; in $(CD_3)_2CO$].

We assume that the formation of **4** and **5** primarily involves the addition of a phosphane or phosphite molecule, respectively, to the metal accompanied by a π/σ-rearrangement of the allyl group in **3b**, as has been demonstrated in the reaction of $C_5H_5Pd(2\text{-}RC_3H_4)$ with PR_3 and $P(OR)_3$[15]. A subsequent hydride-shift leads to a fulvene(hydrido)palladium(II) intermediate, from which, after elimination of 2,3,3-trimethyl-1-butene (detected ^1H-NMR spectroscopically) and addition of a second molecule of L, the fulvene complexes are formed.

That the formation of a 1,2,3,4-tetramethylfulvene ligand from C_5Me_5 is not restricted to palladium as metal atom has been shown by recent investigations on the synthesis of dinuclear $(\mu\text{-}C_5Me_4{-}CH_2)$ titanium complexes[16] as well as by NMR studies on the dynamics of $Ti(C_5Me_5)_2$[17].

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2a, 12081-18-4; **2b**, 73769-66-1; **3a**, 83463-65-4; **3b**, 83463-66-5; **4**, 83463-67-6; **5**, 83463-68-7; PdL_4 (L = PMe_2Ph), 36570-08-8; PdL_4 (L = $PMePh_2$), 24981-80-4; LiC_5Me_5, 51905-34-1.

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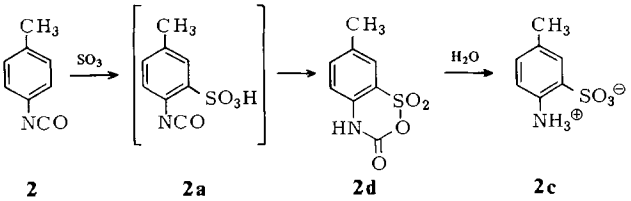
The Sulfonation of Aromatic Isocyanates: Sulfonated *p*-Tolyl Isocyanate—An X-Ray Structure Analysis

By *Gerhard Ballé, Liborius Born, Dieter Dieterich*, Marcel Petinaux,* and *Helmut Reiff*

Investigations on the sulfonation of aromatic mono- and polyisocyanates have shown that compounds containing isocyanate and sulfonic acid functions in one molecule are formed only in those cases in which the sulfo group enters the *ortho* position to the isocyanate group in the aromatic ring. We report here on the structure of sulfonation product **2d** derived from *p*-tolyl isocyanate **2**. Compound **2d** was formed by reaction of **2** with gaseous sulfur trioxide or with chlorosulfuric acid in dichloroethane. **2d** is a pale yellow powder which is practically insoluble in conventional inert organic solvents and is decomposed to the aminosulfonic acid **2c** with evolution of CO_2 on treatment with excess water. The IR spectrum of **2d** shows a sharply resolved group of bands in the region 1200–1400 cm^{-1} (sulfonic acid derivative) and one carbonyl band at 1780 cm^{-1}. Chemically, **2d** behaves like an isocyanatosulfonic acid, *i.e.* it gives the usual reactions of isocyanate and sulfo groups (urethane and urea formation, conversion into the isocyanatosulfonyl chloride or into the salt of the isocyanatosulfonic acid with a tertiary amine).



2 **2a** **2d** **2c**

The carbonyl band in the IR spectrum disappears in each case. The entry of the sulfo group in the *ortho* position to the NCO group can be confirmed by NMR spectroscopic investigations on derivatives. A complete structure elucidation *via* chemical routes seems impossible, since an important structural element characterized by the carbonyl band is destroyed in all reactions.

Since **2d** can be recrystallized from **2**, and also from $POCl_3$ and gives well-formed, sufficiently large crystals of m.p. 183 °C (dec.), the structure could be determined by X-ray diffraction. **2d** proved to be 7-methyl-2,1,4-benzoxathiazin-3(4*H*)-one-1,1-dioxide, a cyclic carbamic acid-sulfonic acid anhydride (Fig. 1). In contrast to the known open-chain carbamic acid-sulfonic acid anhydrides[2], this product is thermally fairly stable. Its formation is favored by the possibility of ring closure to the six-membered heterocycle. This ring system is new. The chemical behavior

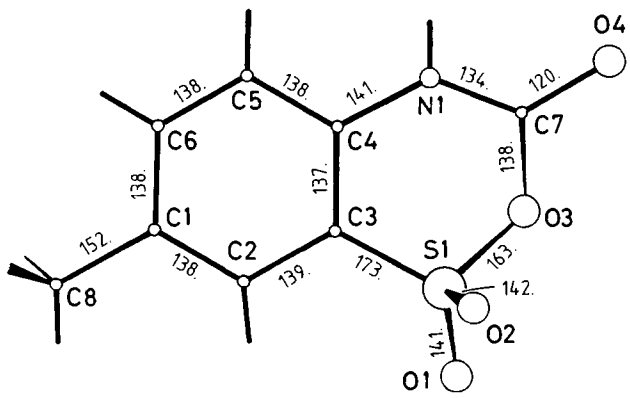


Fig. 1. Molecular structure of **2d** in the crystal including bond lengths in pm (standard deviations: 0.6 pm). Most important angles: C3—S1—O3 99.2(2), S1—O3—C7 120.2(7), O3—C7—N1 115.1(4), C7—N1—C4 126.3(7)°. Deviations from the plane of the aromatic ring: N1 5.5, C7: 47.4, O3: 76.4, S1: −11.8 pm. The annelated oxathiazine ring is thus present in a distorted half-boat form.—All data are average values from the two molecules of the asymmetric unit.

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could be explained in terms of a temperature-dependent equilibrium between **2d** and the open form **2a**. Evidence for such an equilibrium is provided by the IR spectra recorded in solution at high temperatures.

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CAS Registry numbers:
2, 622-58-2; **2d**, 83350-95-2.

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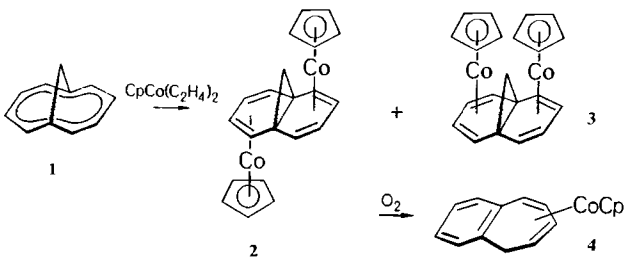
First Metal Complexes of the Norcaradiene Form of 1,6-Methano[10]annulene

By *Peter Mues, Reinhard Benn, Carl Krüger, Yi-Hung Tsay, Emanuel Vogel,* and *Günther Wilke**

The sole transition metal complex of 1,6-methano[10]annulene **1** so far described in the literature is a tricarbonylchromium adduct[1], in which the annulene ligand, in complete contrast to complexes of cycloheptatriene, has benzenoid bonds similar to those in the free annulene **1**. Attempts to trap the norcaradiene derivative tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene, presumed to be in valence tautomeric equilibrium with **1**, by complexation to $Fe(CO)_3$ have hitherto remained unsuccessful[**], although recent *ab-initio* calculations indicate the aromatic system to be only 5 kcal/mol more stable than the tricyclic tautomer[2]. Complexation of the norcaradiene derivative by reaction of **1** with dicarbonyl(cyclopentadienyl)cobalt was also unsuccessful[**].

We have now found that reaction of **1** with η^5-cyclopentadienylbis(ethene)cobalt[3] leads to complexation. Reaction of the two components in pentane at room temperature affords the dark-red, crystalline air-stable complex **2** (35% yield, m.p. (dec.) 108–109 °C) and **3** (<1% yield).



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[+] NMR spectroscopy.

[++] X-ray structure analysis.

[**] Experiments being carried out by Professor Dr. E. Vogel and his research group.

[***] More detailed information on the crystal structure investigation can be obtained on request from the Fachinformationszentrum Energie Physik Mathematik, D-7541 Eggenstein-Leopoldshafen, by quoting the following number CSD 50247, the name of the author and the journal citation.

Proof of the structure and composition is provided in particular by the ^{1}H-NMR spectra: in the case of **2**, in contrast to **3**, they show not only two different Cp groups but also two differently complexed butadiene moieties and bridge H-atoms. The disappearance of the aromaticity through valence isomerization to the norcaradiene derivative in the cobalt complexes manifests itself in the downfield shift of the bridge protons ($\delta = 0.95$ and 1.87 in **2**, $\delta = 1.33$ in **3**) of over 1 ppm in comparison with **1** and in their smaller geminal coupling ($^2J = 1.8$ Hz in **2**), as well as by their $^1J(^{13}C\text{-}H)$ coupling of about 164 Hz. Furthermore, the H,H couplings in the butadiene moieties of **2** and **3** are very similar to those observed for butadiene(Cp)Co[3]. (In **2**, AA′ = 3.8 and 3.7 Hz, and AB = 6.1 and 5.5 Hz, respectively, in **3**, AA′ = 4.2 and AB = 5.4 Hz.) All signals in **2** and **3** could be unequivocally assigned by nuclear Overhauser difference spectroscopy. The resulting structures derived therefrom for **2** and **3** are in complete agreement with the results of crystals structure investigations[***].

The distances between the bridgehead atoms are of particular interest: they are very much shorter than the C-1—C-6 distance in **1** (2.26 Å)[4] being only 1.512(5) Å in **2** and 1.499(5) Å in **3**. This clearly indicates that complexation of **1** is accompanied by cyclopropane ring-closure. The two isomers differ in the geometry of the tricyclic skeleton. In **2**, the diene systems are fixed *exo-endo*, whereas in **3** an *endo-endo* form is present. All CpCo groups π-bonded to this system have identical geometries. However, the molecule **3** has a number of special features and the extremely long CC bonds to the bridge atom C-11 (1.568(5) and 1.573(5) Å) indicate that the molecule is highly strained. In pentane, **2** reacts with atmospheric oxygen with partial decomplexation to give compound **4**. Presumably, **4** is the product of Berson-Willcott rearrangement, which is also observed under thermolytic conditions[5].

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ab initio Calculation of Deformation Densities in Porphyrins

By *Marc Bénard**

Both experimental and theoretical studies of the electron deformation density[1] of organometallic compounds have become increasingly frequent. However, the first high resolution X-ray diffraction study on a porphyrin system (*meso*-tetraphenylporphinatocobalt(II), CoTPP) has only

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recently been reported by *Stevens*[4]. We describe here preliminary results of *ab initio*-SCF calculations of the deformation density distributions in the "low-spin" cobalt(II) porphyrin (CoP) and the "intermediate-spin" iron(II) porphyrin (FeP), which are considered as models for CoTPP and FeTPP.

For CoP, the calculations were carried out on the $^2A_1$ configuration, which can be considered as the ground state. In FeP, the assignment of the ground state is still under discussion: conflicting experimental results indicate that the ground state might correspond either to a $^3A_{2g}$ configuration $(xy)^2(xz)^1(yz)^1(z^2)^2$[13], or to a ^3E_g configuration $(xy)^2(xz)^{1.5}(yz)^{1.5}(z^2)^1$[14], or to a spin-orbit coupling of these two states[15]. We report here the deformation density distribution for the $^3A_{2g}$ state only. Comparison of the computed distribution with that obtained from an X-ray study, which will appear shortly, should give some indication about the nature of the ground state.

The calculated deformation density map computed for CoP in the plane containing the metal atom and one pyrrole ring is displayed in Figure 1 (right). The corresponding map obtained by *Stevens* from the observed X-ray data, which is modeled using a multipole deformation refinement[4], is shown in Figure 1 (left). The difference between the two never exceeds 0.3 e Å^{-3}, except in the close vicinity of the nuclei. Such an agreement can hardly be improved within the framework of a static theoretical investigation.

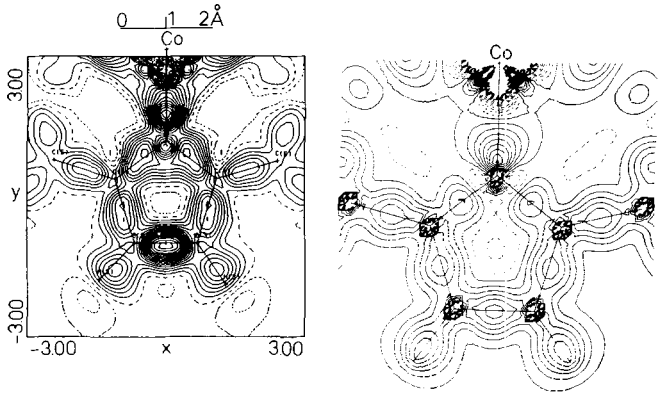

Fig. 1. Right: Computed deformation density for CoP plotted in the plane of the pyrrole ring. Contour intervals 0.10 eÅ^{-3}. Negative contours dashed.—Left: Observed deformation density (modeled) for CoTPP. Contours at 0.05 eA^{-3} with zero and negative contours dashed. Reproduced from [4] with permission of the author.

However, a map in the average molecular plane has little interest for the nature of the ground state of FeP, since the orbital populations in the xy-plane are similar for both the $^3A_{2g}$ and the ^3E_g configurations. Rather, one must consider the population of the d_{z^2} orbital in FeP, which is 2 for the $^3A_{2g}$ state and 1 for the ^3E_g state. The deformation density along the z-axis should therefore be quite different for these two states. A section through the computed deformation density distribution by a plane containing the z axis and bisecting two NFeN (or x0y) angles gave the following for the $^3A_{2g}$ state of FeP:

The computed distribution obtained shows four regions of accumulation. Two of them are localized along the z-axis and the other two along the line perpendicular to 0z bisecting the NFeN angles (in the xy-direction). These four regions of accumulation are similar in height and shape, and correspond to the filled d_{xy} and d_{z^2} orbitals in the $(xy)^2(xz)^{1.5}(yz)^{1.5}(z^2)^2$ configuration. This result is important with regard to the nature of the SCF ground state of FeP. One can reasonably infer that any mixing of the $^3A_{2g}$ state with the ^3E_g state $(xy)^2(xz)^{1.5}(yz)^{1.5}(z^2)^1$ will reduce the peak height along the z-axis, but not along the xy-direction. It can be therefore predicted that any significant dissymmetry between these two directions—should it be found experimentally—would represent a strong argument in favor of a spin-orbit coupling between the $^3A_{2g}$ and ^3E_g states.

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CoP, 32662-36-5; FeP, 32647-22-6.

[1] The electron deformation density distribution $\Delta\rho(r)$ is defined as the difference between a molecular electron density distribution and the superposition of spherically averaged distributions.

[4] E. D. Stevens, *J. Am. Chem. Soc. 103* (1981) 5087.
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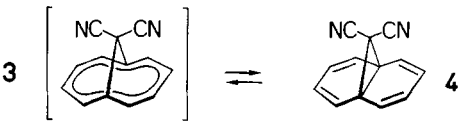
Norcaradiene Valence Tautomer of a 1,6-Methano[10]annulene: Tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene-11,11-dicarbonitrile

By *Emanuel Vogel**, *Thomas Scholl*, *Johann Lex*, and *Georg Hohlneicher*

In memoriam, Otto Bayer

According to the *ab initio* calculations of *Cremer* and *Dick*[1], the Hückel aromatic 1,6-methano[10]annulene and its unknown norcaradiene valence tautomer (tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene) are separated by a free energy difference ($\Delta G = 4.5$ kcal/mol), which is practically equal to that between cycloheptatriene and norcaradiene. It is, therefore, to be expected that under the influence of π acceptor substituents on the methylene carbon atom[5] the postulated equilibrium 1,6-methano[10]annulene-tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene[4] should experience similar displacements to the side of the norcaradiene component as those observed for the cycloheptatriene-norcaradiene equilibrium.



The reaction of **5** with butyllithium and phenyl cyanate affords a transient dicyanide which, as evidenced by ^{1}H-NMR findings, must be **3** and/or **4**. Attempts at the isolation and full characterization of this species have until now been futile due to its pronounced tendency to undergo the Berson-Willcott rearrangement with formation of the known cycloheptatriene derivative **6**. We have now found

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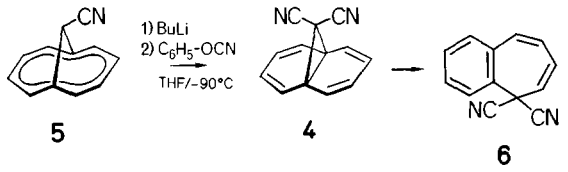
that the dicyanide can be isolated if the reaction product is worked-up below −10 °C and recrystallized at low temperature from dichloromethane; yield 27%. The compound, which occurs as colorless parallelepipeds, readily isomerizes in solution in chloroform [$t_{1/2}$(20 °C) = 28 min] to give **6**; in the crystal it is transformed into **6** only at 65–68 °C.



5 **4** **6**

The temperature independent ^{1}H-NMR spectrum (in CD_2Cl_2) of the dicyanide exhibits an AA'BB' system at $\delta = 6.27$ and 6.43 ($J_{1,2} = 9.64$ and $J_{2,3} = 6.20$ Hz), whose center is shifted by approximately 0.8 ppm to higher field relative to that of the AA'BB'-system of the vinylic protons in 1,6-methano[10]annulene. In the ^{13}C-NMR spectrum the C-1/C-6 signal of the dicyanide ($\delta = 54.5$) is shifted to high field by no less than 59 ppm relative to that of 1,6-methano[10]annulene ($\delta = 113.7$) and, hence, approaches the signal of C-1/C-6 in tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene-11,11-dicarbonitrile ($\delta = 37.3$).

The NMR spectra of the dicyanide are consistent with the norcaradiene structure **4**, but leave open the possibility that the concentration of **3** at equilibrium is up to 10%.

A more precise statement on the maximum concentration of **3** is provided by the electronic spectrum. Whereas 1,6-methano[10]annulene displays the characteristic three band spectrum of a [4+2]annulene [with an intense ($\varepsilon = 68000$) band at 256 nm] the dicyanide exhibits a spectrum consisting of two bands [$\lambda = 243$ nm ($\varepsilon = 6450$), 283 (2400) (in 2-methyltetrahydrofuran)] which in its appearance resembles that of tricyclo[4.4.2.0^{1,6}]dodeca-2,4,7,9-tetraene. A weak shoulder in the region of the long wavelength band of the dicyanide probably arises from **3** ($\leq 1\%$).

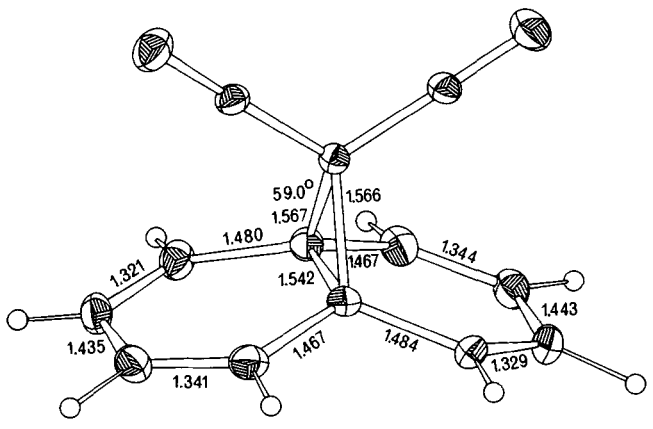


Fig. 2. Molecular structure of **4** in the crystal; bond lengths [Å].

The X-ray structural analysis (Fig. 2) of the dicyanide indicates that this also exists as **4** in the crystal. In contrast to the 11,11-dimethyl and 11-cyano-11-methyl derivatives of 1,6-methano[10]annulene[14], whose structural parameters lie between the values expected for the [10]annulene and norcaradiene structures (C-1–C-6 distance of 1.6–1.8 Å), the dicyanide exhibits a C-1–C-6 distance (1.542Å) corresponding to the length of a cyclopropane bond, and in consequence possesses 1,3-diene-type molecular segments C-2 to C-5 and C-7 to C-10.

The existence of **4**, as well as the recent synthesis of tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene transition-metal complexes by *Wilke et al.*[16] corroborate the statements, chiefly based on theoretical calculations, that the stability relationships in the "arene-olefin equilibrium" 1,6-methano[10]annulene-tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene and in the cycloheptatriene-norcaradiene equilibrium correspond to each other to a remarkable degree.

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[4] E. Vogel, *Pure Appl. Chem. 20* (1969) 237.
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[14] M. Simonetta, *Pure Appl. Chem. 52* (1980) 1597; R. Bianchi, T. Pilati, M. Simonetta, *J. Am. Chem. Soc. 103* (1981) 6426; a structural analysis of **4** at low temperatures is presently being undertaken by M. Simonetta.
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$[Ta_4F_{12}O_6]^{4-}$: A Tetranuclear Fluorooxotantalate(V) with Adamantane Skeleton

By *Jean Sala-Pala, Jacques-E. Guerchais**, and *Anthony J. Edwards*

As mentioned by *Van Wazer et al.*[1] about twenty years ago, "an outstanding challenge in chemistry is the preparation and characterization of families of compounds (ranging from the smallest molecule of the series—the *neso* molecule—to the infinitely large *macro* molecules) based on atoms other than carbon in the spine of the molecule". If we consider group V in this light, most work has been carried out since this date on compounds of the main group, mainly those of phosphorus[2]. With tantalum, and particularly fluorotantalate species, only few studies have been published[3], and in order to fill this gap we recently studied the hydrolysis of $Et_4N[TaF_6]$. The ^{19}F-NMR spectra[4] obtained are rather complicated and suggest formation of several anions made up from the following structural units: $[TaF_6]^-$ ("*neso* molecule"), $[TaF_5O_{1/2}]^-$ (end group), $[TaF_4(O_{1/2})_2]^-$ (middle group) and $[TaF_{3-x}(O_{1/2})_{3+x}]^-$ (x = 0...3; branch groups).

We report here on the complex $(Et_4N)_4[Ta_4F_{12}O_6]$, **1**, whose anion is made up of four *fac*-$[TaF_3(O_{1/2})_3]^-$ branch groups; the complex $(Et_4N)_2[Ta_2F_{10}O]$, **2**, built up from two end groups, has been described previously[4].

Complex, **1**, which was obtained by hydrolysis of **2**, is hygroscopic and its IR spectrum is not significantly different from that of **2** [880 cm^{-1}, vs, ν(TaOTa); 500 cm^{-1}, s, ν(TaF)]. In the ^{19}F-NMR spectrum only a sharp singlet is observed even at low temperature [($CDCl_3$), standard: CF_3CO_2H): $\delta = 50.0 \pm 0.5$] suggesting that all the fluorine atoms are equivalent. The results of an X-ray diffraction analysis of **2** are illustrated in Figure 1a[5]. $[Ta_4F_{12}O_6]^{4-}$ has an adamantane skeleton consisting of four Ta and six

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O atoms (Fig. 1b), and therefore its structure may be compared with that of P_4O_{10} (H form)[2]. However, each Ta atom has three bridging O atoms in a *fac*-arrangement with the octahedron completed by three terminal F atoms. In contrast, the P atoms in P_4O_{10} are pseudotetrahedrally coordinated.

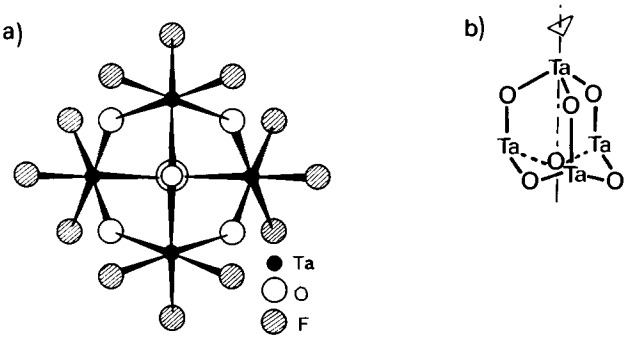

Fig. 1. a) Crystal structure of the anion of $(Et_4N)_4[Ta_4F_{12}O_6]$ **1** (projection along [001]). Interatomic distances and angles (average values): Ta—O 1.93, Ta—F 1.97, Ta...Ta 3.61 Å; Ta—O—Ta 139, O—Ta—O 91, F—Ta—F 87°; b) adamantane skeleton of Ta_4O_6.

Experimental

A solution of **2**[4] in CH_3CN (containing *ca.* < 1% water) under a nitrogen atmosphere is refluxed for 24 h. After cooling, colorless crystals of **1** slowly appear. These are filtered off, washed with ether, and dried *in vacuo*. Yield: 20%.

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CAS Registry numbers:
1, 83380-14-7; **2**, 63871-56-7.

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[5] Orthorhombic crystals, space group Fmm2; $a = 16.56(1)$, $b = 17.95(1)$, $c = 22.43(2)$ Å. Patterson-Fourier techniques; 1599 in independent reflections, $R = 0.055$. The molecular data are influenced by extensive disorder of the C atoms of the cations.

A Novel Route to Phloroglucinols – Synthesis, Structure, and Reactions of [n](2,4)Phloroglucinophanes**

By *Franz Effenberger**, *Karl-Heinz Schönwälder*, and *John J. Stezowski*

Dedicated to Professor Hermann Stetter on the occasion of his 65th birthday

Aldehyde enol ethers can be acylated to β-dicarbonyl- and 1,3,5-tricarbonyl-compounds in very good yields with reactive acid chlorides such as di- and trichloroacetyl chloride, phosgene or malonic acid dichloride **1**[1]. The ketone enol ethers **2** react—except with malonic acid dichloride—analogously; with **1**, the 4-hydroxy-2*H*-pyran-2-ones **6** and/or phloroglucinols **7** are obtained (Table 1). Since the pyranones **6** can be converted into the phloroglucinols **7**[2] the reaction of **2** with **1** enables a generally applicable synthesis of phloroglucinol and its derivatives in very good yields.

The extension of this reaction to enol ethers of cyclic ketones **8** leads to the bicycles **9** and/or **10** and/or the [n](2,4)phloroglucinophanes **11**, which allow interesting conclusions to be drawn about the structure and reaction behavior of metacyclophanes owing to the possibility of tautomerism in the arene moiety (Table 1). Aqueous work-

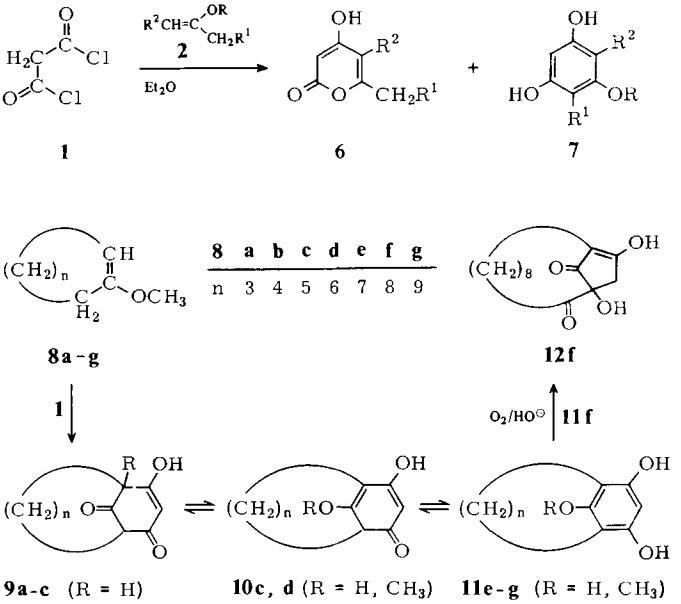

Table 1. 4-Hydroxy-2*H*-pyran-2-ones **6** and phloroglucinols **7** (selection).

2	R	R^1	R^2	**6** + (Yield [%])		**7**	
2a	CH_3	H	H	**5a**	(43)	**7a**	(52)
2b	C_2H_5	H	H	**6a**	(42)	**7b**	(43)
2c	$CH(CH_3)_2$	H	H	**6a**	(24)	**7c**	(65)
2d	$C(CH_3)_3$	H	H	—		**7d**	(79)
2e	CH_3	H	C_2H_5	**6b**	(11)	**7e**	(80)
2f	CH_3	CH_3	CH_3	**6c**	(30)	**7f**	(53)
2g	CH_3	C_2H_5	H	**6d**	(15)	**7e**	(16)

up of **8a—c** and **1** affords the bicycles **9a—c** (yields 84, 88, and 91%, respectively), while work-up of **8a**, **b** and **1** in methanol furnishes the 9,9- and 10,10-dimethylketals of **9a**, **b**, respectively. In the reaction of **8c—g** with **1** the hydrochlorides of the methyl ethers of **10c**, **d** and **11e—g** can be isolated (yields 70, 31, 18, 55, 28%).

The expected competition between the tautomers **9—11** can be deduced from the side views of the X-ray crystallographically determined structures of **9a** (n = 3), **9c** (n = 5), and **11g** (n = 9), where in each case R = H. In **9a** there is a strain-free coupling of 4-cyclohexene-1,3-dione and cyclohexanone in the chair form and in **9c** a combination of 4-cyclohexene-1,3-dione with cyclooctanone in the energetically less favorable chair-chair conformation. In **11g** the twelve-membered ring is almost strain-free and orthogonally coupled with the arene.

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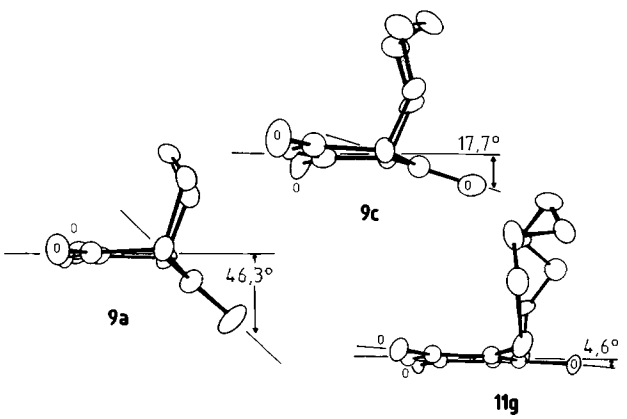
The compounds **9**—**11** show different chemical behavior, depending on ring size and ring strain. The hydrochlorides of **10c** (R = CH_3) and **11f, g** (R = CH_3) with



n = 5, 8, 9 can be cleaved to the corresponding hydroxy compounds **9c** and **11f, g** (R = H) even with water, whereas in the case of **10d** (R = CH_3) and **11e** (R = CH_3), with n = 6, 7, no cleavage of ether takes place even under drastic conditions (conc. HBr). Comparable with the conversion of deoxyhumulone into humulone and its rearrangement to isohumulone[14] is the reaction of **11f** (R = H), whose autoxidation and rearrangement to the obviously more stable bicycle **12f**, however, takes place much more rapidly; this can be explained in terms of a decrease in strain on going from an 11- to a 12-membered ring.

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1, 1663-67-8; **2a**, 116-11-0; **2b**, 926-66-9; **2c**, 4188-63-0; **2d**, 4188-70-9; **2e**, 53110-70-3; **2f**, 41623-41-0; **2g**, 61142-47-0; **6a**, 675-10-5; **6b**, 83436-27-5; **6c**, 31246-34-1; **6d**, 18742-94-4; **7a**, 2174-64-3; **7b**, 28334-98-7; **7c**, 64507-45-5; **7d**, 83436-28-6; **7e**, 83436-29-7; **7f**, 23848-22-8; **8a**, 931-51-1; **8b**, 50438-50-1; **8c**, 50438-51-2; **8d**, 70578-46-0; **8e**, 13659-75-1; **8f**, 57620-91-4; **8g**, 32400-32-1; **9a**, 83436-30-0; **9a** · 9,9-dimethylketal, 83436-31-1; **9b**, 83436-32-2; **9b** · 10,10-dimethylketal, 83436-34-4; **9c**, 83436-33-3; **10d** (R = CH_3), 83436-36-6; **10d** (R = CH_3) · HCl, 83436-35-5; **11e** (R = CH_3), 83436-38-8; **11e** (R = CH_3 · HCl, 83436-37-7; **11f** (R = H), 83436-40-2; **11f** (R = CH_3) · HCl, 83436-39-9; **11a** (R = H), 83436-42-4; **11a** (R = CH_3) · HCl, 83436-41-3; **12f**, 83436-43-5;

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^{13}C-^{13}C and ^{13}C-H Coupling Constants and the Electronic Structure of Cyclopropane, Cyclohexane, and Propane

By *Jürgen Wardeiner, Wolfgang Lüttke*, Rüdiger Bergholz,* and *Reinhard Machinek*

Dedicated to Professor Edgar Heilbronner on the occasion of his 60th birthday

The $^1J_{CC}$ and $^1J_{CH}$ coupling constants of saturated hydrocarbons are almost exclusively governed by the hybridization of the coupling C atoms *via* the Fermi contact term[1]. A complete set of $^1J_{CC}$ and $^1J_{CH}$ values should, therefore, give information about the electronic structure of a molecule, specifically about the hybridization of its C atoms. In order to obtain this information for cyclopropane **1**, cyclohexane **2**, and propane **3** we have determined the complete set of ^1J-values of isotopomers specifically labeled with ^{13}C and ^2H. We evaluated the data comparatively with respect to the different orbital properties arising from the various bond angles.

Table 1. ^{13}C-^{13}C and ^{13}C-H coupling constants [Hz] of **1**, **2**, and **3** [a].

	1	**2**	**3**
$^1J_{CC}$	12.4_0	32.7_0	34.6_5
$^1J_{CH}$	160.4_0	124.6_5	125.3_5 (CH_3) [b] 124.3_5 (CH_2) [b]
$^2J_{CH}$	−2.6	−4.0	—

[a] Mean deviation: ±0.1 Hz. [b] R. E. Wasylishen, T. Schaefer, *Can. J. Chem. 52* (1974) 3247.

Assuming that in CH bonds the non-contact terms hardly contribute to the coupling, the hybrid orbitals and the interorbital angles of all the C atoms can be calculated from the $^1J_{CH}$ data using the Muller-Pritchard equation[2a] and the sum rule[2b] for the s-character. From the orthogonality relationships[3] of molecular groups of type L_2ZL_2' the s-character of the individual C orbitals provides the values of the CCC- and HCH-interorbital angles in **1**, **2**, and **3**. The hybridizations thus obtained (Table 2) are in good agreement with the results of quantum chemical calculations[4].

Table 2. Hybridizations and interorbital angles of **1**, **2**, and **3**.

		1	**2**	**3**	
				CH_2	CH_3
s-Character	CH	0.3208	0.2492	0.2486	0.2506
	CC	0.1792	0.2508	0.2514	0.2483
Hybridization indices	CH	$sp^{2.12}$	$sp^{3.01}$	$sp^{3.02}$	$sp^{2.99}$
	CC	$sp^{4.58}$	$sp^{2.99}$	$sp^{2.98}$	$sp^{3.03}$
Interorbital angles	HCH	118.2°	109.4°	109.3°	109.6°
	CCC	102.6°	109.6°	109.7°	—

An almost ideal sp^3-hybridization is obtained for cyclohexane **2** and propane **3**. In contrast, the particular bonding characteristics of cyclopropane **1** are reflected in the considerably different s-character of the C orbitals of its CH and CC bonds; in consequence, the HCH and CCC interorbital angles deviate markedly from the values expected from ideally sp^3 hybridized C atoms: the cyclopropane CCC interorbital angle of 102.6° indicates that the axes of the hybrid orbitals of **1** are each bent by 21.3° relative to the direct line connecting the nuclei, corresponding to the *bent bonds* model of *Coulson*[4]. This result is experimentally confirmed by X-ray electron density determinations[5] as well as by quantum chemical calculations[4]. It is conspicuous that the experimentally determined CCC bond angles in **2** and **3** are *larger* (**2**: 111.4°, **3**: 112.4°) than the tetrahedral angle, but that the corresponding interorbital angles exhibit only minimal widening. In **1** an opposite deviation of a greater amount is noticeable: the forced reduction of the CCC bond angles from 109.5° to

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60° only causes a reduction of the CCC interorbital angle to 102.6°. Irrespective of whether the CCC bond angle is reduced or widened, the hybrid orbitals of all three hydrocarbons apparently have a strong tendency to retain the ideal tetrahedral angle as far as this is energetically possible, and to limit the orbital following to a minimum. This behavior, at least for saturated hydrocarbons, appears to be valid in general.

As we have found, the CCC coupling constants of aliphatic hydrocarbons can be represented well by the linear relationship (using the data of nine symmetric hydrocarbons).

$$^1J_{CC} = 658 \cdot s_1 \cdot s_2 - 7.9$$

If the s_{CC} data of Table 1 determined from the $^1J_{CH}$ values *via* the sum rule[2b] are inserted into this equation, $^1J_{CC}$ values of 13.2 for **1**, 33.5 for **2**, and 33.2 for **3** result. The (only slight) deviations of these data from the experimental ones (Table 1) provide a measure for the non-contact contributions to the $^1J_{CC}$. Hence, in **1**, **2**, and **3** the ^{13}C-^{13}C coupling actually arises almost completely from the Fermi contact mechanism.

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1, 75-19-4; **2**, 110-82-7; **3**, 74-98-6.

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BOOK REVIEWS

Modern Hot Atom Chemistry and its Applications. By *T. Tominaga* and *E. Tachikawa*, Inorganic Chemistry Concepts 5. Springer-Verlag, Berlin 1981. viii, 154 pp., bound DM 98.00.

The chemistry of hot atoms is dead, long live hot atom chemistry, in its modern and applied version, of course, at least that is what the title of the book suggests. On a closer inspection, however, the reader will inevitably come to the conclusion that the term "modern" means the beginning of the seventies and that the applications seem modest. This is not the fault of the authors. Already by the end of the sixties hot atom chemistry was no longer an individual and uniform field of endeavour, and what appeared to have a future has meanwhile been substantially taken over by physical chemistry, chemistry of the solid state, radiation biology, or radiolabelling chemistry.

One would certainly expect something new on experimental techniques, and it is precisely here that the book is disappointing. A modern book on hot atom Chemistry (HAC) should, for example, devote more than two pages to atomic and molecular beam techniques. Equally disappointing is the treatment of radiochemical separation techniques of the stable labelled molecules which are formed as a final manifestation of a nuclear recoil process. The chromatography has remained at the 1965 level; there is no mention of more sophisticated techniques, such as high-performance liquid chromatography.

The core of the book is the chapter "Characteristics of Hot Atom Reactions". On the whole, the parts on the reactions of hot tritium, halogen, carbon, silicon, germanium, and phosphorus atoms are didactically clear and coherent. A comparison with the reactions of the corresponding thermal atoms would have been useful here, especially as many thermochemical, photochemical, and radiation chemical investigations have now been published, which clearly show the similarities and the differences between the reactions of hot and thermal atoms. The part on "Solid Phase Hot Atom Reactions" is also too short.

In the chapter "Application of Hot Atom Chemistry and Related Topics" the emphasis is obviously on the related topics, since it is difficult to force subjects such as laser isotope separation or NEET (Nuclear Excitation by Electron Transition) into the HAC category. With this broadening of the concept of HAC in mind, it is difficult to see why muonium chemistry is discussed but positronium chemistry is not. Naturally, there are also HAC problems in energy research, but they play a minor role, and the examples confirm this. However, better choices could have

been made, particularly in the case of nuclear fusion. On the whole, the authors' aim to demonstrate the many-sided relationships of HAC with other research sectors is certainly praiseworthy, and has substantially been achieved. The importance of HAC is made obvious in topics such as the unimolecular decomposition of highly excited products, the study of the selectivity and reactivity of unsolvated decay ions, processes for rapid labelling with short-lived radionuclides, the chemical consequences of the radioactive decay and the Auger effect in biomolecules as the starting point for entry into novel areas of selective radiation biology. But all this is touched on only briefly, as if to give the reader no more than a taste. Few will quite get their money's worth (DM 98!), if any, hot atom chemists themselves. Either the book has come out five years too late or it is much too superficial.

Gerhard Stöcklin [NB 563 IE]

Elektrochemie (Electrochemistry) II (taschentext [pocket text] 42) by *C. H. Hamann* and *W. Vielstich*, Verlag Chemie, Weinheim 1981. xv, 428 pp., bound, DM 52.00.

A second volume on the subject of electrochemistry has now appeared in the "taschentext" series, building on Volume I (ionics, electrochemical thermodynamics) which appeared six years ago[*]. The extensive subjects of electrochemical kinetics and applied electrochemistry are now dealt with, each of them taking up about as much space as the whole of the first volume.

At the center of the kinetic treatment of electrode processes is, naturally, the current-voltage curve. The influence of the types of overvoltage on the course of this curve is discussed in detail. Not only simple metal electrodes but also mixed electrodes, semiconductor electrodes, and illuminated semiconductor electrodes are considered.

The chapter on electrochemical measurement techniques leads to the classical steady-state and nonsteady-state methods, the authors obviously being concerned to give a concentrated account of the theoretical foundations. Non-electrochemical techniques for surface analysis are also discussed, including such areas of topical interest as field desorption mass spectroscopy.

Among others, the processes at the hydrogen and oxygen electrodes are discussed as specific examples of electrode processes. The oxygen anode is considered somewhat too briefly; reference should perhaps have been made to a possible third mechanism of redox catalysis (decomposition of electrochemically formed oxides).

In the second part of the volume electrochemical syntheses, galvanic cells, and electrochemical surface techniques are discussed in extensive detail and the reader is acquainted with some modern developments. However, in the chapter on chlorine-alkali electrolysis one would like to find a somewhat more detailed account of the technical prerequisites for the vigorous development that set in 15 years ago with the advent of activated titanium anodes *(Beer)* and perfluorinated ion-exchange membranes, acknowledged perhaps in footnotes. The Monsanto process for the electrosynthesis of adiponitrile has for technical reasons been carried out in undivided cells since the end of the sixties, as has now become known through *Danly's* publications. Unfortunately, there is no mention of *Baizer*, the man who initiated this innovation.

In connection with a possible future hydrogen economy the electrolysis of water and the hydrogen/oxygen fuel cell are discussed in detail. The possibilities of secondary cells are outlined. These sections are particularly well arranged.

The authors' wish to present not only an accurate but also a clear account of the individual fields can be considered as largely achieved, and the few blemishes present hardly affect this over-all impression. (Thus, on p. 15—and then again on p. 39—it is expressly emphasized that the transfer reaction of electrons can be described as a quantum-mechanical tunnelling process. In spite of this, the Butler-Volmer equation on pp. 16—21 is derived precisely on this example with the aid of the Arrhenius equation.)

In spite of the necessary brevity, in most cases the authors succeed in formulating the problems precisely. On the whole, a readable and reliable account of electrochemistry has thus been achieved, which leads directly to the present situation in areas that are very much in a state of flux. The arrangement of the volume, and particularly the figures, is good. The book can be safely recommended to anyone who wishes to become acquainted with modern electrochemistry, and this also applies to the university level, although many students could be put off by the relatively high price.

Fritz Beck [NB 564 IE]

[*] See *Angew. Chem. Int. Ed. Engl. 15* (1976) 447.

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 (Federal Republic of Germany).

Heterocyclic Compounds. Vol. 32, Part 2: Quinolines. Edited by *G. Jones*. John Wiley & Sons, Chichester 1982. xii, 685 pp., bound, £ 70.00.—ISBN 0-471-28055-0

Benzodiazepines. A Handbook. Basic Data, Analytical Methods, Pharmacokinetics and Comprehensive Literature. By *H. Schütz*. Springer-Verlag, Berlin 1982. xii, 439 pp., bound, DM 198.00.—ISBN 3-540-11270-7

Synergetik. Eine Einführung. By *H. Haken*. Springer-Verlag, Berlin 1982. xiv, 382 pp., bound, DM 69.00.—ISBN 3-540-11050-X

Cyclodextrins and Their Inclusion Complexes. By *J. Szejtli*. Akadémiai Kiadó, Budapest 1982. 296 pp., bound, DM 67.50.—ISBN 963-05-2850-9

Vibrations at Surfaces. Edited by *R. Caudano, J.-M. Gilles,* and *A. A. Lucas*. Plenum Press, New York 1982. xii, 585 pp., bound, $ 69.50.—ISBN 0-306-40824-4

Fundamentals of General, Organic and Biological Chemistry. 2nd Edition. By *J. R. Holum*. John Wiley & Sons, Chichester 1982. xvii, 717 pp., bound, £ 19.20.—ISBN 0-471-06314-2

Ellis Horwood Series in Analytical Chemistry: Education and Teaching in Analytical Chemistry. By *G. E. Baiulescu, C. Patroescu,* and *R. A. Chalmers.* Ellis Horwood Limited, Chichester 1982. 190 pp., bound, £ 15.00.—ISBN 0-85312-384-5

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Stabilization of Unusual Oxidation and Coordination States by the Ligands OSF_5, $OSeF_5$, and $OTeF_5$

By Konrad Seppelt*

Compounds with the ligands OSF_5, $OSeF_5$, and $OTeF_5$ are now known for most of the chemical elements. The ability of these ligands to stabilize the highest valency levels of the central atoms to which they are bound is unsurpassed by any other polyatomic ligand. Examples are $Xe(OTeF_5)_6$, $Te(OTeF_5)_6$, $W(OTeF_5)_6$, and $U(OTeF_5)_6$ or $I(OTeF_5)_5$ and $Br(OSeF_5)_3$. Because of the ligands' size and internal bonding they hardly ever form bridges, and in this respect they differ from fluorine, although they do share the latter's high electronegativity.

1. Introduction

The hexafluorides SF_6, SeF_6, and TeF_6 belong to the standard textbook repertoire. Their structure, bonding relationships, and lack of reactivity have meant that SF_6 in particular has become a typical example for perfluorinated compounds. Attempts to coax SF_6 into chemical reactions founder on its almost complete inertness. The coordination number of 6, relatively high for sulfur, precluded any attack by bases, which would have led to a temporary increase in coordination. Thus, SF_6 is stable to sodium hydroxide solutions up to temperatures of several hundred °C.

On the other hand, attack by acids, *e.g.* H^+ or AsF_5, should be easier because abstraction of fluoride would entail a reduction of the coordination number. There is hardly any experimental data, but it should be noted that substituted SF_6, *e.g.* CH_3—SF_5, is likewise completely inert to bases, but is immediately attacked by AsF_5, even at very low temperatures[1].

A comprehensive chemistry could not therefore be established starting from SF_6. But TeF_6, which can be substituted by bases, should be better because it can increase its coordination number beyond 6. However, the development of the above-mentioned ligands actually followed quite a different course:

Careful fluorinations of the elements or of the dioxides produced, quite unexpectedly, compounds such as $FOSF_5$[2], $FOSeF_5$[3], F_5SO—OSF_5[4], F_5SeO—$OSeF_5$[3], and F_5TeO-TeF_5[5]. It was not until the probably accidental discovery of pentafluorooxotelluric acid, $HOTeF_5$, by *Engelbrecht* and *Sladky*[7] and the similarly accidental discovery of its selenium analog $HOSeF_5$ by *Seppelt*[8] that the potential of the ligands was understood. It was only later that pentafluorooxosulfuric acid, $HOSF_5$, was shown to exist. This, however, has no preparative significance because of its instability[9].

2. The Acids $HOSF_5$, $HOSeF_5$, and $HOTeF_5$

New classes of compounds are usually discovered by chance. The reaction of barium tellurate with fluorosulfuric acid was ostensibly intended to yield the (still) unknown TeO_2F_2[7], in the same way that SeO_2F_2 is obtained in good yield from $BaSeO_4$ and FSO_3H[11]. However, in the tellurium system mainly $HOTeF_5$ was obtained[6, 7, 10]. This finding, which at the time was surprising, is now explained by the fact that hexavalent tellurium always strives to attain the coordination number 6. This tendency becomes still clearer when the hydrolysis of TeF_6[12, 13] or the solvolysis of $Te(OH)_6$ in HF are investigated[13–16]. Practically all the intermediate species $(HO)_xTeF_{6-x}$ have been detected.

$HOTeF_5$ is formed according to[7]

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$$Te(OH)_6 + 5\,FSO_3H \rightarrow 5\,H_2SO_4 + HOTeF_5$$

The analogous selenic acid $HOSeF_5$ is formed, however, from SeO_2F_2 with an increase in the coordination number[8, 17, 18]:

$$3\,SeO_2F_2 + 4\,HF \rightleftharpoons 2\,HOSeF_5 + H_2SeO_4$$

This reaction establishes selenium as a true intermediate between sulfur and tellurium, because Se species with the coordination numbers 4 and 6 exist side by side. Sulfonyl fluoride SO_2F_2, on the other hand, is a strikingly inert compound with no tendency whatever to increase its coordination. Thus it is not surprising that $HOSF_5$ is unstable, releasing HF, and must be synthesized by more devious routes[9, 19]:

$$SOF_4 + ClF \xrightarrow{CsF} ClOSF_5 \xrightarrow[-Cl_2]{HCl} HOSF_5$$

The three compounds $HOXF_5$ are justifiably regarded as acids. On the one hand, a wide variety of XOF_5-salts is known (see Section 3), and on the other the acid strength of $HOTeF_5$ in glacial acetic acid has been measured directly and has been found to lie between those of HCl and HNO_3[20, 21]. The acid strength is certainly an expression of the inductive effect caused by the accumulation of fluorine atoms.

The octahedral structure of the molecules is most readily shown by their ^{19}F-NMR spectra of the AB_4 type (see Section 9). This indicates that the proton can rotate freely on the NMR time scale. Despite this, there is apparently a small fourfold torsion barrier of the proton as evident from satellite bands of the OH stretching and deformation vibrations in $HOSeF_5$ and $HOTeF_5$[19]. This phenomenon has not, so far, been subjected to a closer investigation. To the best of our knowledge no other example of a fourfold torsion barrier has been found (see Fig. 1).

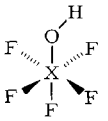


Fig. 1. Molecular model of $HOXF_5$. The similarity of OH and F results in an almost regular octahedral structure. This is reflected in many physical properties. The estimated intramolecular H...F distances are as follows: $HOSF_5$ 201, $HOSeF_5$ 232, $HOTeF_5$ 238 pm. No indication of an intramolecular H...F bridge has been established.

Formally derived from the chalcogen hexafluorides by replacement of one fluorine atom by an OH group, the pentafluorooxochalcogen(VI) acids are still virtually spherical molecules and consequently have both high melting points and vapor pressures. The melting points can be sharply depressed by the presence of impurities. Moreover, in the case of $HOSeF_5$ in particular, the vibrational spectra of the $OSeF_5$ skeleton degenerate almost to those of a regular octahedron, because the mass of the OH group and the strength of its bond to selenium do not essentially differ from those of the fluorine atoms[22]. The vibrational spectra of $HOTeF_5$ have a far greater number of bands[23].

The thermal stability of the three acids varies considerably[19]:

$$HOSF_5 \xrightarrow{-60\,^\circ C} HF + SOF_4$$

$$HOSeF_5 \xrightarrow{290\,^\circ C} HF + 1/2\,O_2 + SeF_4$$

$$HOTeF_5 \xrightarrow{>310\,^\circ C} HF + (TeOF_4)_n + TeF_6 + TeF_4 + \cdots$$

Below $-60\,^\circ C$ $HOSF_5$ is only kinetically stable to reduction of coordination. The somewhat lower stability of the hexavalent state of selenium limits the existence of $HOSeF_5$, whereas $HOTeF_5$ has none of these weaknesses and thus decomposes only at very high temperatures, and even then in uncharacteristic fashion.

These thermal stabilities also indicate, for example, the range of application of the ligands OSF_5, $OSeF_5$, and $OTeF_5$. Whereas $OTeF_5$ can be utilized most widely, closely followed in this respect by $OSeF_5$, OSF_5 compounds are only obtainable in a few selected cases.

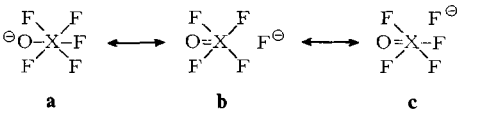
3. The Anions XOF_5^-, the Oxofluorides $O{=}XF_4$, and their Dimers $F_4XO_2XF_4$

It will come as no surprise that the strong acids $HOSeF_5$ and $HOTeF_5$ are easily converted into salts[24–28]. In the case of $HOSeF_5$ a degree of care must be exercised because of the high oxidizing power of the hexavalent selenium; for example, $K^+SeOF_5^-$ can only be obtained from potassium fluoride and not from potassium chloride[26]. Salts of $HOSF_5$ are obtained directly from SOF_4[29, 30]:

$$CsF + SOF_4 \rightleftharpoons Cs^+SOF_5^-$$

However, this reaction only proceeds with CsF, RbF, and KF. Presumably the lattice energy of sodium fluoride is too high, and that of the hypothetical $Na^+SOF_5^-$ too low, as is frequently the case with sodium salts of fluorinated anions.

The salts contain the isolated anion XOF_5^-, as can readily be shown by vibrational spectroscopy. The high frequency of the OX stretching vibration is striking, and a charge distribution



a **b** **c**

can thus be assumed[22, 26, 27, 30]. The low frequency of the axial X—F stretching vibration is particularly noticeable, so that the middle of the three mesomeric formulas **b** must have a high weighting.

The stronger mutual influence between the *trans*-atoms in the octahedral system is readily explained by the current bonding models: predominantly the T_{1u} molecular orbitals (*e.g.* in SF_6)—and thus the *p*-atomic orbitals of the central atom—form the bond. *trans*-Atoms share the same *p*-orbital. This *trans*-effect is also noticeable in the ^{19}F-NMR spectra (see Section 9). Here, mainly the signals of the axial fluorine atoms in XOF_5^- salts are shifted considerably relative to those of the free acids[26].

The alkali metal salts dissolve in acetonitrile without decomposition. $Ag^+TeOF_5^-$ forms ion-pairs in concentrated CH_3CN solution[27]. No exact structural data are as yet

available for these salts. Because of the cubic crystal symmetry (Fm3m) of the $SeOF_5^-$ salts, the anions must be statistically oriented[122]. *In the* $TeOF_5^-$ *salts the fluorine and oxygen atoms are likewise indistinguishable, although the crystal symmetry is rhombohedral in these cases*[28].

Due to the charge distribution in the anions, the oxofluorides $O{=}XF_4$ appear to be structurally preformed in the salts. In the case of sulfur there is a true equilibrium[29]. However, the oxofluorides cannot be released from the potassium, rubidium, and cesium salts of $SeOF_5^-$ and $TeOF_5^-$. This can only be achieved with $Na^+SeOF_5^-$ and $Li^+TeOF_5^-$, because of their lower lattice energies[31-33].

$$2\,K^+SeOF_5^- \xrightarrow[10^{-2}\ mbar]{400\ ^\circ C} 2\,KF + SeO_2F_2 + SeF_6$$

$$Na^+SeOF_5^- \xrightarrow[10^{-2}\ mbar]{150\ ^\circ C} NaF + SeOF_4$$

$$2\,Na^+TeOF_5^- \xrightarrow[10^{-2}\ mbar]{300\ ^\circ C} cis\text{-}Na_2TeO_2F_4 + TeF_6$$

$$2\,Li^+TeOF_5^- \xrightarrow[10^{-2}\ mbar]{130\ ^\circ C} 2\,LiF + (TeOF_4)_2$$

The salts of the lighter alkali metals have to be made by a more complicated method, *e.g.*[33]:

$$(CH_3)_3Si{-}OSeF_5 + Na^+OSi(CH_3)_3^- \rightarrow (CH_3)_3Si{-}O{-}Si(CH_3)_3 + Na^+SeOF_5^-$$

$SeOF_4$ has a similar structure to SOF_4, namely trigonal bipyramidal with the doubly bonded oxygen in the equatorial plane. Above $-100\,^\circ C$ it dimerizes spontaneously to $F_4SeO_2SeF_4$ and thus eludes the unfavorable coordination number 5[33,34]. Apparently the equilibrium

$$F_4SeO_2SeF_4 \rightleftharpoons 2\,SeOF_4$$

only occurs at higher temperatures[35]. Monomeric $TeOF_4$ is not obtained at all, but appears always as the dimeric $F_4TeO_2TeF_4$[32,33] or the polymeric $(TeOF_4)_n$[36,37].

The dimer $F_4TeO_2TeF_4$ is, moreover, formed in virtually quantitative yield from $B(OTeF_5)_3$ by vacuum pyrolysis[38]. The structure of the dimers has been closely examined by various methods[33,38,39]. A striking feature is the short distance between the chalcogen atoms, although no bonding between them can be assumed (see Fig. 2).

Whereas SOF_4 serves as the direct or indirect starting material for many OSF_5 compounds, $SeOF_4$ and $(TeOF_4)_2$ have not been studied under this aspect. Virtually all the $OSeF_5$ and $OTeF_5$ compounds are prepared directly or indirectly from $HOSeF_5$ and $HOTeF_5$.

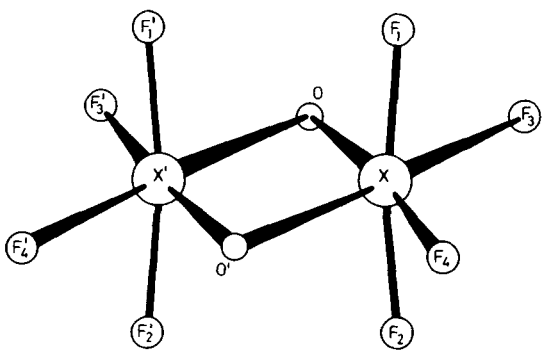


Fig. 2. Molecular model of $(SeOF_4)_2$ and $(TeOF_4)_2$ based on electron diffraction measurements. *In spite of the close proximity of the chalcogen atoms* (267 and 293 ppm) bonding interaction between them is not presumed (from [38]).

4. The Oxides $F_5X{-}O{-}XF_5$, the Peroxides $F_5XO{-}OXF_5$, and the Trioxide $F_5SO{-}O{-}OSF_5$

The oxides $F_5X{-}O{-}XF_5$ can be regarded as the anhydrides of the acids $HOXF_5$. But no reaction is known in which mutual conversion takes place in a manner even approaching the smoothness that the name "anhydride" suggests. According to another tradition, monodentate electronegative (see Section 5) ligands are named pseudohalides, and the peroxides $F_5XO{-}OXF_5$ would accordingly be the corresponding pseudohalogens. This name, too, has only formal significance. However, the two types of compounds have a structural significance in their own right. The oxides $F_5X{-}O{-}XF_5$ are, moreover, the initial members of a series of compounds, see below. Lastly, $F_5S{-}O{-}SF_5$, $F_5SO{-}OSF_5$, and $F_5SeO{-}OSeF_5$ were among the first compounds to have OXF_5 groups at all (see Section 1).

These compounds can be prepared in various ways:

$$SF_4 + SF_5OF \xrightarrow{h\nu} F_5S{-}O{-}SF_5\ [40,41]$$

$$SF_4 + OF_2 \xrightarrow{h\nu} F_5S{-}O{-}SF_5\ [42]$$

$$SF_5Cl + O_2 \xrightarrow{h\nu} F_5S{-}O{-}SF_5\ [43]$$

$$XO_2 + F_2/N_2 \longrightarrow F_5X{-}O{-}XF_5 \quad X = S\ [44],\ Se\ [45],\ Te\ [46]$$

$$Xe(OSeF_5)_2 \xrightarrow{>100\ ^\circ C} F_5Se{-}O{-}SeF_5\ [47]$$

$$SF_4 + SeF_5OF \longrightarrow F_5S{-}O{-}SeF_5\ [48]$$

$$SO_2(OTeF_5)_2 + K^+TeOF_5^- \longrightarrow F_5Te{-}O{-}TeF_5\ [6]$$

The oxides $F_5X{-}O{-}XF_5$ almost achieve the kinetic stability of the corresponding hexafluorides.

Little is known about the physiological action of $F_5S{-}O{-}SF_5$[49]: this seems of significance because $F_5S{-}SF_5$ is extremely toxic.

The structures of these fluorooxides were derived from electron diffraction measurements[42,50], since single crystal data have not yet been obtained because of the low melting points of the material. The bond angle at the oxygen ($140-145\,^\circ$) is relatively large, probably because of the repulsion between the fluorine atoms. The eclipsed arrangement of the fluorines, which contributes to the repulsion, has been interpreted in terms of a $(pd)_\pi$ bonding model[42,50].

These oxide fluorides are only the simplest members of a series, such as *e.g.* *cis*-$F_5SO{-}SF_4{-}OSF_5$[40,51], *cis*- and *trans*-$F_5TeO{-}TeF_4{-}OTeF_5$[52,53], *cis*- and *trans*-$F_2Te(OTeF_5)_4$[52,55], $FTe(OTeF_5)_5$[52,53], $Te(OTeF_5)_6$[52,53], and $(TeOF_4)_n$[36]. All heavy atoms in these compounds are six coordinated, are linked by oxygen bridges, and the remaining valences are filled by fluorine atoms. So far, $F_5S{-}O{-}SeF_5$ is the only known compound of this type with different chalcogen atoms[48].

The peroxides $F_5XO—OXF_5$ are, of course, substantially more reactive than the oxides. Interestingly, a few clean synthetic methods are available for their preparation: small quantities of F_5SOOSF_5 and $F_5SeOOSeF_5$ were originally prepared by fluorinating SO_2 and SeO_2, respectively.

$$2\,ClOXF_5 \xrightarrow{h\nu} Cl_2 + F_5XO—OXF_5 \quad X = S, Se, Te \;[56]$$

$$Xe(OXF_5)_2 \xrightarrow{h\nu} Xe + F_5X—O—O—XF_5 \quad X = Se, Te \;[17]$$

The structures of the peroxides have not been as closely investigated as those of the oxides[57]. One striking feature is that the OOX-angle is much smaller (102–110°) compared to the XOX angles in the compounds $F_5X—O—XF_5$ (140–145°). The peroxide bond can be regarded as unusually strong by virtue of the electron attraction of the XF_5 groups, the strength increasing in the sequence S < Se < Te, as indicated by the position of the peroxide stretching vibrations in the Raman spectra[22,58]. Despite this, in a few cases the peroxides act as transfer reagents for OXF_5 groups:

$$F_5SO—OSF_5 + SO_2 \longrightarrow F_5SO—SO_2—OSF_5 \;[51,59]$$

$$F_5SO—OSF_5 + SO_2 \xrightarrow{h\nu} F_5SO—SO_2F \;[51,60]$$

$$F_5SO—OSF_5 + C_6H_6 \longrightarrow C_6H_5—OSF_5 + SOF_4 + HF \;[61]$$

$$F_5SO—OSF_5 + CF_3O—OCF_3 \longrightarrow 2\,CF_3O—OSF_5 \;[51]$$

$$F_5SO—OSF_5 + FSO_2O—OSO_2F \longrightarrow 2\,FSO_2O—OSF_5 \;[51]$$

$$F_5SeO—OSeF_5 + F_2 \longrightarrow 2\,FOSeF_5 \;[3]$$

$$F_5SeO—OSeF_5 + FSO_2O—OSO_2F \longrightarrow 2\,FSO_2—OSeF_5 + O_2 \;[45]$$

There is little doubt that the majority of these reactions require radical cleavage of the peroxide bond, many take place upon UV irradiation. The ESR signals of the radicals $\cdot OSeF_5$ and $\cdot OTeF_5$ have been thoroughly analyzed[17].

$F_5SO—SF_4—O—OSF_5$ and $F_5SO—SF_4—O—O—SF_4—OSF_5$ can even be observed in the reaction of $FOSF_5$ with SF_4 in presence of ogygen[40].

The potential of the SF_5 group to stabilize unusual bonding is demonstrated by the preparation of the trioxide $F_5SO—O—OSF_5$, which can be obtained from SF_5OOH and F_2[62] or from SF_5Cl and O_2[63]. Kinetic studies of $F_5SO—O—OSF_5$ have led to an optimization of the preparative conditions[63–67].

The synthesis of the peroxoacid SF_5OOH and its halogen derivatives is highly unconventional:

$$ClOSF_5 + FCO—O—O—COF \xrightarrow{h\nu} FCO—O—OSF_5 \;[62]$$

$$FCO—O—OSF_5 + H_2O \longrightarrow HF + CO_2 + HOOSF_5 \;[63,68]$$

$$HOOSF_5 + ClF \longrightarrow ClOOSF_5 \;[62]$$

$$HOOSF_5 + F_2 \longrightarrow FOOSF_5 \;[62]$$

The last-mentioned compounds are thermally relatively unstable, and represent virtually unique systems. Only the analogues with CF_3 in place of SF_5 exist. Clearly SF_5OOCl and SF_5OOF are highly reactive compounds, which can undergo numerous reactions with retention of the SF_5OO group[68–70].

5. Electronegativity of the Ligands OSF_5, $OSeF_5$, and $OTeF_5$; Stabilities of Their Compounds

Recently the extraordinary stability of the xenon derivatives (see Section 7) has raised the question of the group electronegativity. However, electronegativity is an ambiguous concept, especially if it is applied to a group.

Several possibilities have been proposed for the determination of group electronegativity: the chemical shift of the ^1H-NMR of the methyl protons of $CH_3—OSeF_5$ relative to those of CH_3F, CH_3Cl, CH_3Br, and CH_3I[71], the difference between the chemical shifts of the methyl and methylene protons in $C_2H_5—OTeF_5$[72], the preference for equatorial positions in the substitution of IF_5 in the compounds $IF_x(OTeF_5)_{5-x}$ and $IF_x(OSeF_5)_{5-x}$[73,74], Mössbauer data, and ^{125}Te- and ^{129}Xe-NMR resonance measurements[75]. In all cases the electronegativity is found to be very high for OXF_5, and with two particular methods actually higher than that of fluorine[71,73,74]. It is quite possible that the accumulation of five fluorine atoms at the chalcogen atom produces an extreme electron deficiency there, extending as far as the oxygen and beyond. The electronegativity of this oxygen atom would then exceed that of the fluorine atom, because fluorine, despite its electron attraction is able to restore electron density *via* π bonds. This seems to be much less possible with oxygen in OXF_5 compounds. It is also conspicuous that the Lewis acidity of $B(OTeF_5)_3$ is greater than that of BF_3 or of $B(OR)_3$, but comparable with that of BCl_3[36].

It may well be that the OXF_5 groups are more electronegative than fluorine. However, the stability of corresponding fluorine compounds is unsurpassed (see Section 7):

$$XeF_4 \xrightarrow{300-600\,^\circ C} XeF_2 + F_2$$

$$Xe(OTeF_5)_4 \xrightarrow{72\,^\circ C} Xe(OTeF_5)_2 + F_5TeO—OTeF_5$$

To a first approximation it can be assumed that the Xe—F and Xe—O bond strengths in XeF_4, XeF_2, $Xe(OTeF_5)_4$, and $Xe(OTeF_5)_2$ are similar. The differences in stability thus result from the fact that the peroxide $F_5TeO—OTeF_5$ is formed much more readily than F_2. In fact, the peroxide bond is extremely strong (see Section 4).

OXF_5 compounds can undergo various decomposition reactions. Loss of the whole ligand with peroxide formation always takes place when the bond between the central atom Y and the ligand is weak. Here the tellurium compounds are slightly more stable than the others:

$$Y(OXF_5)_2 \rightarrow Y + F_5XO—OXF_5$$
Stability $OTeF_5 > OSeF_5 > OSF_5$

$$Y(OXF_5) \rightarrow YF + O{=}XF_4,\ 1/2(OXF_4)_2 \text{ or } 1/n(OXF_4)_n$$
Stability $OTeF_5 > OSeF_5 > OSF_5$

$Y(OXF_5)_2 \rightarrow Y{=}O + F_5X{-}O{-}XF_5$

$YF(OXF_5) \rightarrow Y{=}O + XF_6$

Stability $OTeF_5 > OSeF_5 > OSF_5$ (?)

$Y(OXF_5) \rightarrow YXF_5 + 1/2\,O_2$

Stability $OSF_5 > OSeF_5 > OTeF_5$

The elimination of $O{=}XF_4$, leaving one fluorine behind is encountered particularly with coordinatively unsaturated or very electropositive central atoms: $B(OTeF_5)_3$, $Ti(OSeF_5)_4$, $K^+SOF_5^-$. This decomposition is the weak point of many OSF_5 compounds, because $O{=}SF_4$ is particularly readily eliminated.

Coordinatively highly saturated compounds, such as $I(OTeF_5)_5$, and the hypothetical compounds $Os(OTeF_5)_6$, $Re(OTeF_5)_7$, and others, eliminate TeF_6 and $F_5TeOTeF_5$ with the formation of oxo derivatives such as $O{=}I(OTeF_5)_3$, $O{=}Os(OTeF_5)_4$, and $O_2Re(OTeF_5)_3$, respectively. The differences in stability between $OTeF_5$, $OSeF_5$, and OSF_5 derivatives are not known exactly because of the almost complete absence of the OSF_5 and the $OSeF_5$ compounds.

The elimination of oxygen is rare and so far only found in $F{-}OXF_5$, $F_5XO{-}OXF_5$, and $F_5SO{-}O{-}OSF_5$:

$F{-}OXF_5 \rightarrow XF_6 + 1/2\,O_2$

$F_5XO{-}OXF_5 \rightarrow F_5X{-}O{-}XF_5 + 1/2\,O_2$

Stability $OSF_5 > OSeF_5 > OTeF_5$ in both cases

$F_5SO{-}O{-}OSF_5 \rightarrow F_5SO{-}OSF_5 + 1/2\,O_2$

However, in these cases the OSF_5 ligand is the most stable, and $F_5SeO{-}O{-}OSeF_5$ and $F_5TeO{-}O{-}OTeF_5$ remain as yet unknown.

But in general, the $OTeF_5$ compounds usually prove to be the most stable, followed by the $OSeF_5$ and then, at some distance, by the OSF_5 compounds.

On the other hand, work with volatile $OTeF_5$ compounds is highly unpleasant from the physiological point of view. The body counters the incorporation of tellurium by expiring $Te(CH_3)_2$, which smells very strongly of garlic[76]. This process can persist for months. There is apparently a natural metabolism for incorporated selenium, because expiration of $Se(CH_3)_2$ subsides after only a few days. No problems of this type are encountered with OSF_5 compounds.

6. Main-Group Derivatives

Apart from the alkali metal salts which contain the ion XOF_5^-, an abundance of OXF_5 compounds are known; these are listed completely in Table 1. Nearly all these compounds can be formally produced by the replacement of F by OXF_5; practically all of these compounds are extremely volatile and some are astonishingly resistant to hydrolysis.

All this indicates that the OXF_5 groups cause very little intermolecular interaction. Whereas the small fluorine atom has a notorious tendency to form fluorine bridges (only in highly fluorinated compounds is this not observed), OXF_5 ligands virtually never form bridges. In particular, because of their spherical form and very weak intermolecular forces, compounds with several OXF_5 groups have a pronounced tendency to sublime, *i.e.* they have a rather high melting point together with a high volatility. This behavior culminates in the almost spherical compounds $HOXF_5$, $C(OSeF_5)_4$, $Si(OTeF_5)_4$, $Te(OTeF_5)_6$, $W(OTeF_5)_6$, and $U(OTeF_5)_6$. Thus, $Te(OTeF_5)_6$ already sublimes at 110 °C and melts at 242 °C, and is a pure molecular compound with a molecular weight of 1567[52,53]!

The only two main-group compounds in which OXF_5 groups may possibly form bridges are $Br(OSeF_5)_3$[47] (m.p. = 19 °C) and $I(OTeF_5)_3$[83] (m.p. = 44 °C). Both are highly viscous liquids above their melting points. In the fluorine analogues, bridging has been established for BrF_3 and is presumed for IF_3.

The methods of preparation of OXF_5 compounds are many. Although the acids $HOXF_5$ are certainly not always the most elegant starting materials, a few synthesic examples involving them may nevertheless be cited.

$HOTeF_5 + KCl \rightarrow HCl + K^+TeOF_5^-$ [24, 77]

$HOSeF_5 + KF \rightarrow HF + K^+SeOF_5^-$ [26]

$3\,HOTeF_5 + BCl_3 \rightarrow 3\,HCl + B(OTeF_5)_3$ [36, 37]

$2\,HOSeF_5 + XeF_2 \rightarrow 2\,HF + Xe(OSeF_5)_2$ [101]

$HOTeF_5 + SO_3 \rightarrow HOSO_2{-}OTeF_5 \xrightarrow{FSO_3H} FSO_2{-}OTeF_5$ [6, 10]

$2\,HOSeF_5 + 4\,SO_3 \rightarrow FSO_2{-}O{-}SO_2{-}OSeF_5 + 2\,HSO_3F + SeO_2F_2$ [81]

$HOTeF_5 + Sn(CH_3)_4 \rightarrow (CH_3)_3Sn{-}OTeF_5 + CH_4$ [82]

The high oxidation potential of hexavalent selenium restricts the usefulness of $HOSeF_5$ because it decomposes chlorides oxidatively, and thus only fluorides and oxides can be used. $HOTeF_5$, which has a lower tendency to oxidize, is decidedly better. This difficulty can partly be avoided by using $Hg(OSeF_5)_2$, which is itself prepared from HgF_2 and $HOSeF_5$ (see Section 7). This reacts gently with chlorides in inert solvents:

$O{=}SeCl_2 + Hg(OSeF_5)_2 \rightarrow HgCl_2 + O{=}Se(OSeF_5)_2$ [83]

$2\,AsCl_3 + 3\,Hg(OSeF_5)_2 \rightarrow 3\,HgCl_2 + 2\,As(OSeF_5)_3$ [86]

$CCl_4 + 2\,Hg(OSeF_5)_2 \rightarrow 2\,HgCl_2 + C(OSeF_5)_4$ [71]

The method is rather complicated because of the difficulties involved in the preparation of $Hg(OSeF_5)_2$ and $Hg(OTeF_5)_2$.

$OTeF_5$ compounds can be prepared particularly elegantly using the boron compound $B(OTeF_5)_3$[36,37]. Unfortunately, the analogues of selenium and sulfur are not available. Here are a few of the many possible examples:

$AsF_3 + B(OTeF_5)_3 \rightarrow BF_3 + As(OTeF_5)_3$ [82]

$3\,XeF_4 + 4\,B(OTeF_5)_3 \rightarrow 4\,BF_3 + 3\,Xe(OTeF_5)_4$ [99, 110]

$3\,SbF_5 + 2\,B(OTeF_5)_2 \rightarrow 2\,BF_3 + 3\,F_3Sb(OTeF_5)_2$ [90]

The advantage of this method is that the readily volatile and noncorrosive BF_3 can be easily removed from the reaction mixture. The use of the silyl compound can replace the unknown boron compound in the case of $OSeF_5$ to a limited extent.

Table 1. OSF_5, $OSeF_5$ and $OTeF_5$ compounds of the main-group elements.

Group 1 [a]	X
$Li^+OXF_5^-$ [26, 33, 77]	Se, Te
$Na^+OXF_5^-$ [26, 33, 77]	Se, Te
$K^+OXF_5^-$ [7, 24, 26, 77]	S, Se, Te
$Rb^+OXF_5^-$ [26, 26, 77]	Se, Te
$Cs^+OXF_5^-$ [24, 26, 27, 29, 30, 77]	S, Se, Te
Group 3	
$B(OTeF_5)_3$ [36, 37]	
$CsB(OTeF_5)_4$ [37]	
Group 4	
$C(OSeF_5)_4$ [71]	
$CH_x(OXF_5)_{4-x}$ [24, 25, 71, 78]	Se, Te
$CF_3—OSF_5$ [40]	
$C_2H_5—OTeF_5$ [25]	
$FCH_2CH_2—OSF_5$ [41]	
$FClCH—CH_2—OSF_5$ [41]	
$CF_2H—CH_2—OSF_5$ [80]	
$CF_3—CH_2—OSF_5$ [79]	
$C_2F_5—OSF_5$ [41]	
$CFCl_2—CCl_2—OSF_5$ [41]	
$c\text{-}C_5F_8—OXF_5$ [41, 48]	S, Se
$C_2H_5O—CO—CH_2—OTeF_5$ [25]	
$C_6H_5—OSF_5$ [61]	
$p\text{-}R\text{-}C_6H_4—OSF_5$ [61]	
$FCO—OXF_5$ [48, 80]	S, Se
$CF_3CO—OSeF_5$ [81]	
$(CH_3)_3Si—OXF_5$ [33, 82]	Se, Te
$Si(OTeF_5)_4$ [82]	
$(CH_3)_3Ge—OTeF_5$ [82]	
$(CH_3)_3Sn—OTeF_5$ [82]	

Group 5	X	
$NO_2—OSeF_5$ [83]		
$P(OTeF_5)_3$ [84]		
$O=P(OTeF_5)_3$ [85]		
$POF_2—OXF_5$ [86, 74]	Se, Te	Se, Te
$As(OXF_5)_3$ [76, 79]	Se, Te	Se, Te
$As(OTeF_5)_5$ [87]		
$Sb(OTeF_5)_3$ [89]		
$Sb(OTeF_5)_5$ [89]		
$F_4SbOTeF_5$ [90]		
$F_3Sb(OTeF_5)_2$ [90]		
Group 6		
$HOOSF_5$ [62, 68, 69]		
$FOOSF_5$ [62]		
$ClOOSF_5$ [62]		
$O(OSF_5)_2$ [45, 62-64]		
$(OXF_5)_2$ [3, 4, 17, 47, 56-58, 92]	S, Se, Te	
$Alkyl O—OSF_5$ [70, 91]		
$CF_3O—OSF_5$ [51]		
$FSO_2—O—OSF_5$ [51]		
$FCO—O—OSF_5$ [63, 80]		
$OC(OOSF_5)_2$ [69, 91]		
$FSO_2—OXF_5$ [6, 10, 40, 43-45, 51, 60]	S, Se, Te	
$FSO_2—O—SO_2—OSeF_5$ [81]		
$ClSO_2—OTeF_5$ [6]		
$HOSO_2—OTeF_5$ [6, 10]		
$SO_2(OXF_5)_2$ [6, 10, 51, 59]	S, Te	
$SF_5—OXF_5$ [40-44, 48, 50, 59]	S, Se	
$cis\text{-}BrCH_2—SF_4—OSeF_5$ [93]		
$cis\text{-}SF_4(OSF_5)_2$ [40]		
$SF_5O—SF_4—O—OSF_5$ [40]		
$F_5SO—SF_4—O—SO_2—OSF_5$ [59]		
$CF_3O—SF_4—OSF_5$ [40]		
$CF_3O—SF_4—O—OSF_5$ [40]		
$O=Se(OSeF_5)_2$ [83]		
$SeF_5—O—SeF_5$ [42, 45, 47, 48, 50]		
$cis\text{-}SeF_4(OSeF_5)_2$ [88]		
$Te(OTeF_5)_4$ [52, 53, 75]		
$Te(OTeF_5)_6$ [52, 53, 75]		
$F_5Te—O—TeF_5$ [6, 23, 37, 43, 46, 50]		
$F_xTe(OTeF_5)_{6-x}$ [52-55, 86]		

Group 7	X
$FOXF_5$ [3, 40, 41, 48, 94-96]	S, Se, Te
$ClOXF_5$ [17, 47, 94, 95, 97]	
$BrOXF_5$ [47, 83]	Se, Te
$Br(OSeF_5)_3$ [47]	
$RbBr(OSeF_5)_4$ [83]	Se, Te
$I(OTeF_5)_3$ [83]	
$O=I(OTeF_5)_3$ [73, 74]	
$I(OTeF_5)_5$ [73, 74]	
$F_xI(OXF_5)_{5-x}$ [73, 74]	Se, Te
Group 8	
$Kr(OTeF_5)_2$ [98, 99]	
$Xe(OXF_5)_2$ [47, 100-104]	Se, Te
$FXe—OXF_5$ [101, 104-106]	Se, Te
$Xe—OTeF_5^+AsF_6^-$ [107-109]	
$F_5SeO—Xe—OTeF_5$ [17, 104]	
$Xe(OTeF_5)_4$ [99, 110]	
$Xe(OTeF_5)_6$ [98, 99]	
$O=Xe(OTeF_5)_4$ [75, 98, 99]	
$O=XeF_x(OTeF_5)_{4-x}$ [98, 99]	

[a] The salts $NH_4^+OSeF_5^-$ [26] and $C_5H_5NH^+OTeF_5^-$ [24, 77] can be included here.

$$[(CH_3)_3Si]_3N + 4HOSeF_5 \rightarrow NH_4^+SeOF_5^- + 3(CH_3)_3Si—OSeF_5$$ [33]

$$(CH_3)_3SiCl + HOTeF_5 \rightarrow HCl + (CH_3)_3Si—OTeF_5$$ [82]

$$(CH_3)_3Si—OSeF_5 + Na^+OSi(CH_3)_3^- \rightarrow (CH_3)_3Si—O—Si(CH_3)_3 + Na^+SeOF_5^-$$ [33]

To substitute chlorides by $OSeF_5$ one may also start from $ClOSeF_5$:

$$ICl_3 + 3ClOSeF_5 \rightarrow I(OSeF_5)_3 + 3Cl_2$$ [83]

Since HCl is not produced, there is no danger of reducing the hexavalent selenium.

On the other hand, $FOSF_5$ is one of the most important starting compounds for the introduction of the OSF_5 group, usually in the absence of a better alternative. $FOSeF_5$ can sometimes be used for the same purpose:

$$3FOSeF_5 + 2Br_2 \rightarrow BrF_3 + 3BrOSeF_5$$ [47]

$$FOSeF_5 + SF_4 \rightarrow F_5S—O—SeF_5$$ [48]

$$FOSF_5 + CH_2=CH_2 \rightarrow FCH_2—CH_2—OSF_5$$ [41]

$$FOSF_5 + CH_2=CF_2 \rightarrow CF_3—CH_2—OSF_5$$ [79]

The peroxide $F_5SO—OSF_5$ also serves as a source of the OSF_5 group:

$$2F_5SO—OSF_5 + 2SO_2 \rightarrow FSO_2—O—OSF_5 + SO_2(OSF_5)_2 + SOF_4$$ [51, 39]

$$F_5SO—OSF_5 + C_6H_6 \rightarrow C_6H_5—OSF_5 + SOF_4 + HF$$ [61]

Otherwise the incorporation of the OSF_5 group presents the greatest difficulties. SF_5Cl is actually often used as a starting material:

$$2SF_5Cl + O_2 \rightarrow Cl_2 + F_5SO—OSF_5$$ [33]

The synthesis of highly sensitive compounds containing the $OOSF_5$ group deserves particular consideration (see Section 4).

Most of the above-mentioned syntheses are simple substitution reactions. However, the reactions with $FOXF_5$ are also oxidations. Also the xenon derivatives can be used to introduce the OXF_5 group oxidatively:

$$TeF_4 + Xe(OTeF_5)_2 \rightarrow cis,trans\text{-}F_4Te(OTeF_5)_2 + Xe$$ [52, 53]

$$I(OTeF_5)_3 + Xe(OTeF_5)_2 \rightarrow I(OTeF_5)_5 + Xe$$ [73, 74]

The derivatives of the OXF_5 compounds often manifest the typical properties of the elements in very pronounced

form, such as the Lewis acidity of $B(OTeF_5)_3$ and the kinetic stability of $C(OSeF_5)_4$. Solid NO_2—$OSeF_5$ contains ions ($NO_2^+SeOF_5^-$), while in the gaseous state it is covalent (NO_2—$OSeF_5$). Besides CF_3O—O—OCF_3, F_5SO—O—OSF_5 is the only known trioxide. The valency of the stable halogen derivatives increases in a well known manner:

$$FOSeF_5 \triangleq ClOSeF_5 < Br(OSeF_5)_3 < I(OTeF_5)_5$$

7. Noble Gas Derivatives

The special position of the OXF_5 ligands is most striking in compounds of the noble gases. The corresponding compounds are the most stable covalent derivatives of XeF_2, and so far the only covalent derivatives of XeF_4, $XeOF_4$, and XeF_6.

The stable bivalent derivatives can be synthesized in several ways:

$$XeF_2 + HOXF_5 \rightarrow 2HF + Xe(OXF_5)_2 \quad X = Se, Te \quad [17, 100-102]$$

$$3XeF_2 + 2B(OTeF_5)_3 \rightarrow 2BF_3 + 3Xe(OTeF_5)_2 \quad [111]$$

$$3XeF_2 + 2SeOF_2 \rightarrow 2Xe + Xe(OSeF_5)_2 \quad [112]$$

The synthesis of $Xe(OSeF_5)_2$ from $SeOF_2$ and XeF_2 is of particular interest, since the difficult preparation of $HOSeF_5$ can be avoided in this way.

$Xe(OSeF_5)_2$ and $Xe(OTeF_5)_2$ are readily sublimable pale yellow solids stable up to 100 °C. The semisubstituted derivatives are yellow liquids and are formed in an equilibrium reaction.

$$XeF_2 + Xe(OXF_5)_2 \rightleftharpoons 2FXe—OXF_5 \quad X = Se, Te \quad [101, 104-106]$$

$$Xe(OSeF_5)_2 + Xe(OTeF_5)_2 \rightleftharpoons 2F_5SeO—Xe—OTeF_5 \quad [17, 104]$$

It is not surprising that it has also been possible to detect F_5SeO—Xe—$OTeF_5$ by ^{129}Xe-NMR spectroscopy. With the same method it has been shown that Lewis acids remove the fluorine atom and not the $OTeF_5$ group from $FXeOTeF_5$[109]:

$$FXe—OTeF_5 + AsF_5 \rightarrow XeOTeF_5^+AsF_6^-$$

The compounds of tetra- and hexavalent xenon are unique. They were prepared from XeF_4, XeF_6, and $XeOF_4$, in each case with $B(OTeF_5)_3$, and provide insight into the structural behavior of higher valent xenon.

$$3XeF_4 + 4B(OTeF_5)_3 \rightarrow 4BF_3 + 3Xe(OTeF_5)_4 \quad [99, 110]$$

$$XeF_6 + 2B(OTeF_5)_3 \rightarrow 2BF_3 + Xe(OTeF_5)_6 \quad [98, 99]$$

$$3XeOF_4 + 4B(OTeF_5)_3 \rightarrow 4BF_3 + 3O{=}Xe(OTeF_5)_4 \quad [98, 99]$$

Structurally the red, crystalline $Xe(OTeF_5)_6$ is a derivative of the monomeric, gaseous, lemon-yellow XeF_6 and not of the tetrameric or hexameric solid XeF_6, because the $OTeF_5$ ligands show little tendency toward bridge formation.

Since $Xe(OTeF_5)_6$ is isomorphous with rhombohedral $Te(OTeF_5)_6$, it is even possible to comment on the distortion of the octahedral environment of the xenon atom: this must be a C_{3v} or D_{3d} distortion, as postulated for gaseous XeF_6[99].

The colorless $O{=}Xe(OTeF_5)_4$ surpasses the yellow $Xe(OTeF_5)_4$ *in its thermal stability, whereas* XeF_4 *is more* stable than $XeOF_4$. These phenomena still require explanation.

All the intermediate members, $O{=}XeF_x(OTeF_5)_{4-x}$, between $O{=}XeF_4$ and $O{=}Xe(OTeF_5)_4$ can be detected by ^{129}Xe spectroscopy. This has not yet been possible for the systems XeF_6—$Xe(OTeF_5)_6$ and XeF_4—$Xe(OTeF_5)_4$.

$OTeF_5$ would also be the best candidate for a krypton-oxygen bond. Indeed, even at −196 °C cocondensation of KrF_2 and $B(OTeF_5)_3$ leads to an immediate reaction, but only Kr, BF_3, and F_5TeO—$OTeF_5$ are found[99]. Nevertheless, the clean occurrence of F_5TeO—$OTeF_5$ permits the conclusion that a krypton compound is formed, if only as an intermediate. An uncontrolled fluorination by the extremely aggressive krypton fluoride should yield at least a little TeF_6.

8. Transition-Group Derivatives

Table 2 lists all the known OXF_5 derivatives of the transition elements. Strikingly, no OSF_5 derivatives are known. Evidently the abstraction of fluoride from the ligand with formation of SOF_4 occurs too easy. The same decomposition reaction is also observed for many $OSeF_5$ compounds, for example in the systems $F_xTi(OSeF_5)_{4-x}$ and $F_xW(OSeF_5)_{6-x}$[113]. It thus happens that most of the derivatives originate from the $OTeF_5$ group. The ligand-transfer reagent here is nearly always $B(OTeF_5)_3$.

The elements of the first transition period have a tendency to adopt a coordination number of 4, even when fluorides such as VF_5 and CrF_5 are directly substituted.

$$3VF_5 + 4B(OTeF_5)_3 \rightarrow 3O{=}V(OTeF_5)_3 + 4BF_3 + 3TeF_6$$

$Ti(OTeF_5)_4$ is a rare example of a tetrahedral oxygen coordination to titanium. However, an increase in coordination is observed with $Cs_2Ti(OTeF_5)_6$[114]. The larger central atoms tungsten and uranium permit relatively simple formation of the heavy molecules $W(OTeF_5)_6$ and $U(OTeF_5)_6$, although in the case of the tungsten compound WF_5 must be used as the starting material[115, 118, 119].

Table 2. $OSeF_5$- and $OTeF_5$ compounds of transition metals.

Group 1+2	4	5	6	7+8
$Ag^+OTeF_5^-$ [27, 72]	$Ti(OTeF_5)_4$ [113, 114]	$O{=}V(OSeF_5)_3$ [113, 115]	$O_2Cr(OSeF_5)_2$ [113, 115]	O_3Re—$OTeF_5$ [120]
$Au(OTeF_5)_3$ [120]	$Cl_xTi(OTeF_5)_{4-x}$ [114]	$O{=}V(OTeF_5)_3$ [113, 115]	$O_2Cr(OTeF_5)_2$ [113, 115]	$O_2Re(OTeF_5)_3$ [115]
$Hg(OSeF_5)_2$ [17, 26, 77]	$Cs_2Ti(OTeF_5)_6$ [114]	$Nb(OTeF_5)_5$ [115]	$O{=}Mo(OTeF_5)_4$ [115]	$O{=}Os(OTeF_5)_4$ [115]
$Hg(OTeF_5)_2$ [17, 26, 77]		$Ta(OTeF_5)_5$ [115]	$O{=}MoF_3$—$OTeF_5$ [116]	
CH_3Hg—$OTeF_5$ [77]			$W(OTeF_5)_6$ [115]	$U(OTeF_5)_6$ [118, 119]
			$F_xW(OTeF_5)_{6-x}$ [115-117]	$F_xU(OTeF_5)_{6-x}$ [118]
			$ClW(OTeF_5)_5$ [113]	

$WF_5 + B(OTeF_5)_4 \rightarrow W(OTeF_5)_6 + "W(OTeF_5)_4"$
$WF_6 + B(OTeF_5)_3 \rightarrow F_xW(OTeF_5)_{6-x}$

Apparently the intermediate $W(OTeF_5)_5$ disproportionates readily, as is also known for WF_5, whereas WF_6 only undergoes substitution as far as $FW(OTeF_5)_5$[115-117].

It is surprising that molybdenum prefers the coordination number 5; $O{=}Mo(OTeF_5)_4$ is the end product detected[115]. It shares this property with rhenium, which gives $O_2Re(OTeF_5)_3$ as the only stable substitution product, a yellow liquid with still unknown geometry at the rhenium[115]. $O_2Re(OTeF_5)_3$ and $O_3Re{-}OTeF_5$ are the only OXF_5 compounds of a heptavalent central atom. Intermediate octavalent osmium(VIII) compounds tend to decompose to OsO_4, whereas heptavalent and hexavalent osmium fluorides and oxide fluorides all yield $O{=}Os(OTeF_5)_4$, a crystalline product that occurs in a wide variety of colors (black, amethyst, blue, green)[115]. Structure analysis of a uniformly green crystal revealed the composition $O{=}Os(OTeF_5)_4 \cdot 3\,TeF_4$ (see Section 12). In the systems $F_xOs^{VI}(OTeF_5)_y$ and $F_xOs^{VII}(OTeF_5)_y$, red and green intermediates are also found, but could not be isolated in pure form.

As is also observed in other aspects of the chemistry of these elements, the series of the highest-valence compounds is suddenly interrupted at iridium. Only the relatively "normal" derivatives of silver(I), mercury(II), and gold(III) have been found so far. $Au(OTeF_5)_3$ seems to be one of the rare cases with trigonal planar coordination of oxygen at gold: the X-ray structure analysis has not yet been performed. $Hg(OSeF_5)_2$ and $Hg(OTeF_5)_2$ apparently dissolve as molecules in nonpolar solvents but as ions in polar solvents, as has been demonstrated by ^{19}F-NMR spectroscopy[28,27] (see Section 9).

Of the actinoids only $U(OTeF_5)_6$ and its derivatives $F_xU(OTeF_5)_{6-x}$ are known (cf. Fig. 7).

9. NMR Spectroscopy

Of the routine analytical procedures ^{19}F-NMR spectroscopy of the OXF_5 compounds is the most important, since the ^{19}F nucleus has a high sensitivity, 100% natural abundance, and a wide chemical shift range. The OXF_5 ligands always give rise to AB_4 spectra (Fig. 3), recognized by two strong groups of lines (the B_4 part) and a dispersed and weaker group of lines (the A part). In $OSeF_5$ compounds ^{77}Se satellites with a coupling constant of *ca.* 1100 Hz are always observed as well, and in $OTeF_5$ compounds there are also ^{125}Te satellites (*J ca.* 3600 Hz) and very weak ^{123}Te satellites (*J ca.* 3300 Hz).

The spectra are nearly always highly resolved, *i.e.* all the individual transitions can be identified. Even when there is a very large separation between the A and the B_4 parts, the systems never degenerate into the trivial doublet-quintet pattern of a simple AB_4 spectrum.

The coupling constant $J(AB_4)$ varies only within narrow limits, *ca.* 150–160 Hz for OSF_5[121-124], *ca.* 215–230 Hz for $OSeF_5$[125], and *ca.* 175–195 Hz for $OTeF_5$[72,125,126]. Using a simple procedure it can be derived from any high-resolution spectrum[125]. Computer simulation is not really necessary, even though is does provide numerically somewhat more exact values. The signals of OSF_5 and $OSeF_5$ are always found at lower fields relative to $CFCl_3$. Those of homologous compounds (*e.g.* $ClOSF_5$, $ClOSeF_5$) are similar enough to be confused with one another if there were not the ^{77}Se satellites in the selenium compounds. The signals of the $OTeF_5$ groups are always found at higher field relative to $CFCl_3$.

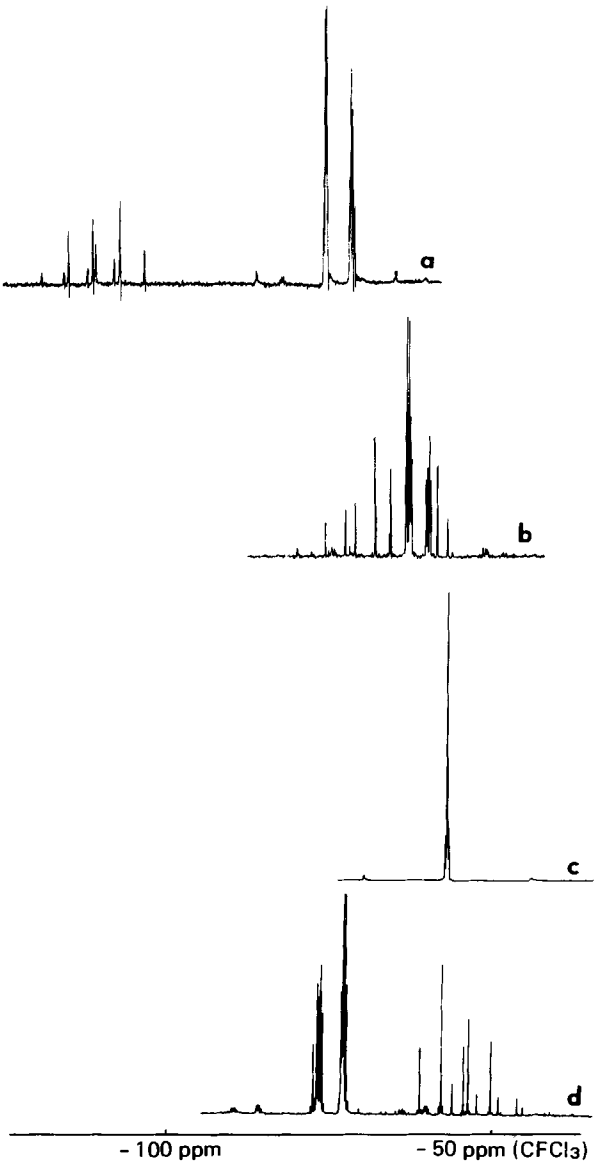


Fig. 3. Typical AB_4 spectra of OXF_5 compounds: a) $NO_2^+OSeF_5^-$ (in acetonitrile), A and B_4 parts are well separated; b) $HOSeF_5$ (in $CFCl_3$), a spectrum still easily recognizable as an AB_4 system; c) $F_5SeO{-}OSeF_5$ (pure liquid), the A and B_4 parts practically coincide; d) $CF_3CO{-}OSeF_5$ (pure liquid, C—*F* resonances at $\delta = +76$ have been omitted), part A eventually occurs to the right of part B_4.
The ^{77}Se satellites are clearly visible in all the spectra.

The chemical shift of the equatorial fluorines (B_4 part) of all three groups varies only little on oxygen substitution, whereas that of the axial fluorine atom varies very sensitively (see Fig. 3)[125]. For very simple $Z{-}OXF_5$ compounds the chemical shift of the axial fluorine correlates well with the electronegativity of Z[125]. In these simple derivatives the A part always occurs at lower field than the B_4 part. In more complicated compounds, such as $B(OTeF_5)_3$

and many others, the reverse is often the case. In a few borderline cases [F_5XO—OXF_5, $Br(OSeF_5)_3$, $CrO_2(OSeF_5)_2$, *etc.*] the A and B_4 parts coincide almost exactly (see Fig. 3). The spectrum then degenerates more or less to a single line. Since, however, the coupling constants of ^{77}Se or ^{125}Te to A and B_4 are different, these small satellite subspectra are sometimes more informative than the main spectra.

Coupling to nuclei outside the OXF_5 group is also observed. In such cases the coupling constant to the equatorial fluorine atoms is always much larger than that to the axial fluorine atom, and coupling to the latter is often not observed at all. The profusion of OXF_5 compounds also inspired NMR studies of other nuclei, such as ^{31}P[86], ^{129}Xe[75, 99, 104, 109, 115], and ^{125}Te[16, 75, 109]. Because of the importance of the OXF_5 group in xenon chemistry the development of ^{129}Xe-NMR spectroscopy was closely linked with preparative $OSeF_5$ and $OTeF_5$ chemistry (see Fig. 4).

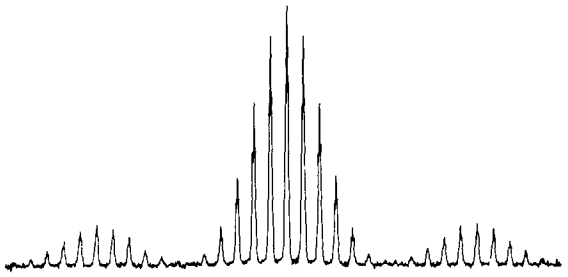


Fig. 4. ^{129}Xe-NMR spectrum of $O{=}Xe(OTeF_5)_4$. The ^{129}Xe nucleus couples with 16 equatorial fluorines, 4 axial fluorines, and 4 tellurium atoms of the isotope ^{125}Te: satellite spectrum (from [99]).

10. Mass Spectroscopy

The mass spectra of these compounds, which are mainly volatile, often reveal the molecular composition. Experimentally, the sample introduction path must be kept short. If, moreover, hydrolysis of the substance can be avoided the effort is rewarded by highly informative mass spectra (see Fig. 5). A weak molecular peak is nearly always observed, whereas loss of an entire OXF_5 group yields an intense fragment.

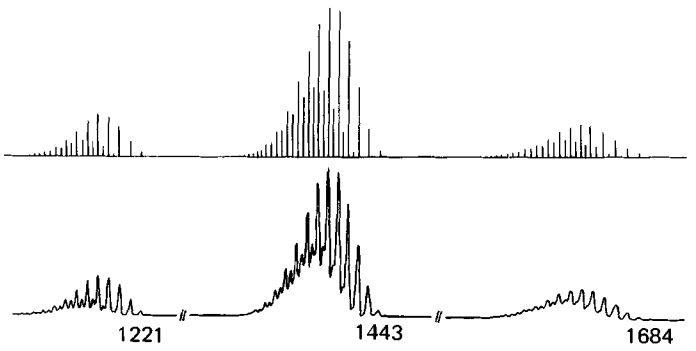


Fig. 5. Mass spectrum of $U(OTeF_5)_6$ (bottom). The section above $m/z = 1200$ shows the ions $FU(OTeF_5)_4^+$ (1221), $U(OTeF_5)_5^+$ (1443), and $U(OTeF_5)_6^+$ (1684). The isotope distribution in species with four, five, and six tellurium atoms extends theoretically over 50—70 mass units and can only be calculated by computer (top) (from [118]).

$O{=}XF_4$ is usually cleaved off next, so that, for example, the fragments $U(OTeF_5)_5^+$ and $FU(OTeF_5)_4^+$ are produced from $U(OTeF_5)_6$[118]. Presumably $ReO_2(OTeF_5)_3$ and $OsO(OTeF_5)_4$ undergo a different fragmentation: in these cases TeF_5-groups are subsequently split off, while Os—O or Re—O bonds are retained; this may perhaps be an indication of the special stability of the OsO and ReO bonds, even under mass-spectroscopic conditions[115].

The isotopic distribution of up to six tellurium atoms and up to four selenium atoms together with the isotopic distribution of the other elements, lead to extremely complicated peak groups, which often are superimposed on each other (see Fig. 5[118]) or refs [113, 116]. The simulation of this isotopic distribution is only possible with the aid of a computer, but it does have considerable informative value. High resolution mass spectroscopy is, however, rather useless, since virtually all the subpeaks originate from a multitude of isotope combinations.

The cumulative mass defect of several heavy atoms makes exact counting of the peaks difficult. The peaks are generally found several tenths of a mass unit too low; moreover, comparison spectra for species with $m/z > 1000$ are not exactly routine.

The mass-spectroscopic examination of nonvolatile compounds provided evidence of volatile decomposition products; thus the existence of the oxofluoride $SeOF_4$ and the nonexistence of $TeOF_4$ under similar conditions were demonstrated for the first time[31-33].

11. Other Analytical Methods

Mass spectra are often able to replace *elemental analysis* to some degree. The latter gets difficult because of the volatility and hydrolytic sensitivity of the substances and because of the difficulty of exactly determining selenium and tellurium in presence of fluorine and other heavy metals.

OXF_5 compounds can be readily detected by *vibrational spectroscopy* if they are neither too aggressive for the IR cell material nor too sensitive to laser light in the recording of Raman spectra, such as *e.g.* $Xe(OTeF_5)_6$. Often the Raman spectra are easier to obtain, because the substances can be sealed *in vacuo* into glass or quartz tubes. The selection of the typical OXF_5 bands on the basis of local C_{4v} symmetry then permits the assignment of less common stretching frequencies such as Xe—O, Br—O, U—O, or Au—O.

12. Crystal Structure Analyses

The molecular structure of the OXF_5 compounds can often be derived from the aforementioned physical methods. However, a few crystal structure analyses have been undertaken, namely for $Xe(OSeF_5)_2$[103], *trans*-$F_2Te(OTeF_5)_4$[54, 55], $Te(OTeF_5)_6$[52, 53], $U(OTeF_5)_6$[119], $O{=}Mo(OTeF_5)_4$[115], and $O{=}Os(OTeF_5)_4 \cdot F^- \cdot TeF_3^+ \cdot 2TeF_4$[115].

Single crystals susceptible to hydrolysis are best prepared by vacuum sublimation, though this process is notorious for the disorder it produces. This problem is enhanced in particular by the spherical shape of the ligands.

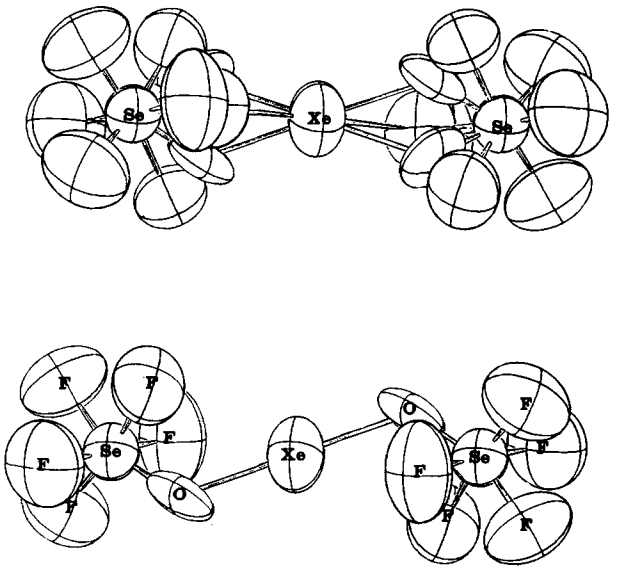


Fig. 6. Crystal structure analysis of $Xe(OSeF_5)_2$. The superimposition of the three molecular orientations, as they occur statistically in the crystal, is shown at the top. Below, one molecular orientation is shown. The assignment of the various fluorine atoms to individual molecular arrangements is arbitrary, but arises from the nearly regular octahedral shape of the $OSeF_5$ part (from [103]).

The disorder is sometimes systematic in nature, as in $Xe(OSeF_5)_2$ (see Fig. 6). Here three molecules are superimposed, but one molecule can be singled out. If the disorder is not so obvious, the whole X-ray analysis often fails, as with the $SeOF_5^-$ salts of the cations K^+, Rb^+, Cs^+, and NH_4^+[22]. The cubic symmetry Fm3m requires a completely disordered arrangement of the anion. In the case of $NO_2^+SeOF_5^-$ (likewise Fm3m) the cation and the anion are disordered[127]. Even in the absence of systematic disorder the peripheral fluorine atoms appear with very large vibrational parameters (see Fig. 7), caused certainly by a combination of molecular vibrations and disorder.

Another problem encountered in crystal structure analysis is the absorption by heavy atoms, which is only alleviated by the application of the usual absorption corrections. Nevertheless, the value of crystal structure analyses

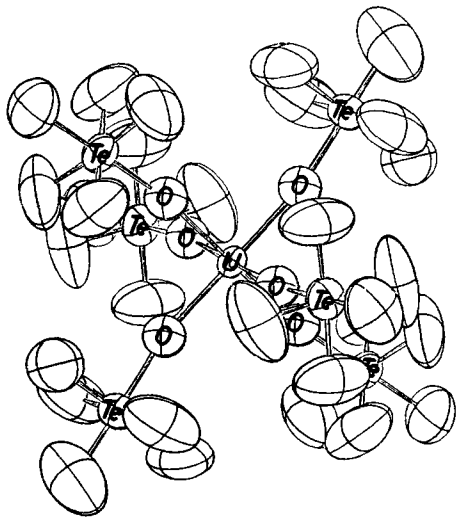


Fig. 7. Crystal structure of $U(OTeF_5)_6$. The peripheral fluorine atoms apparently exhibit large thermal motions, as indicated by the large vibrational ellipsoids. The U—O—Te bridge, with an angle of *ca.* 170°, is almost linear (from [119]).

is undisputed. For example, two precise structure analyses are available for the two modifications of $Te(OTeF_5)_6$[52,53]. Since $Xe(OTeF_5)_6$ has been proven to be isomorphous with the rhombohedral form of $Te(OTeF_5)_6$, valuable conclusions could be drawn about its molecular structure, although only powder diffraction data on $Xe(OTeF_5)_6$ were available[99].

A crystal structure analysis is also available for $U(OTeF_5)_6$ (see Fig. 7). The bond angle U—O—Te (*ca.* 170°) is much larger than the corresponding Te—O—Te angle (*ca.* 139°) in both crystallographic modifications of $Te(OTeF_5)_6$. This difference must reflect the different bonding relationships [(p—f)π bonding?]. Unfortunately, up to now no crystal structure analysis has been reported for $W(OTeF_5)_6$, because the crystals exhibit an almost plastic behavior.

$U(OTeF_5)_6$ and the two modifications of $Te(OTeF_5)_6$ have different crystal symmetries, although the molecular configurations are similar, indeed almost identical (Fig. 8).

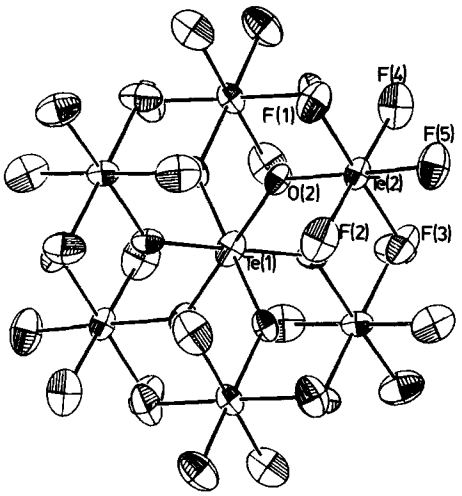


Fig. 8. Crystal structure of $Te(OTeF_5)_6$, rhombohedral modification. The complete enclosure of the core of the molecule by peripheral fluorines determines the stability of this compound to hydrolysis. The Te—O—Te angle (ca. 140°) is strikingly small (cf. Fig. 7) (after [53]).

The packing behavior of these giant spherical molecules is apparently governed by slight deviations from sphericity. All packings can, however, be derived from the hexagonal closest packing of spheres by slight displacements[53].

13. Summary and Outlook

The ligands $OSeF_5$ and $OTeF_5$ represent extremely interesting monovalent ligands which stabilize unusual oxidation states and coordination numbers. The OSF_5 has a limited applicability and can be well compared with the OCF_3 group, as shown by the instability of $HOSF_5$ and $HOCF_3$[128,129] but also by the existence of $SF_5—O—O—O—SF_5$ and $CF_3—O—O—O—CF_3$[130,131].

Hitherto the interest in these ligands has concentrated principally on "binary" compounds of the type $Y(OXF_5)_n$. The particular properties of these ligands have hardly been used for special purposes but it may be expected that, in future, more complicated systems will provide insight into unusual structure relationships. The crystal structure analysis of $O{=}Os(OTeF_5)_4 \cdot F^- \cdot TeF_3^+ \cdot 2\,TeF_4$ may be cited as

an accidental result (Fig. 9). This compound occurs as a by-product in the preparation of $O{=}Os(OTeF_5)_4$ and has been thoroughly studied because of its relatively good crystalline properties[115]. The $O{=}Os(OTeF_5)_4$ molecules are attached like lanterns on a string by F^- bridges to the polymeric $TeF_3^+(TeF_4)_2$ chain.

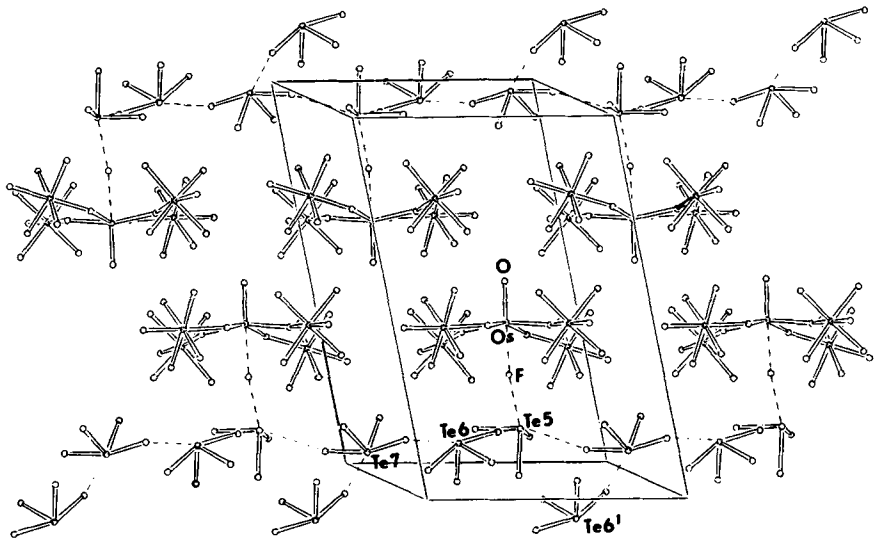


Fig. 9. Crystal structure analysis of $O{=}Os(OTeF_5)_4 \cdot F^- \cdot TeF_3^+ \cdot 2TeF_4$. The compound is formed as a by-product in the preparation of $O{=}Os(OTeF_5)_4$ [115]. The TeF_3^+ and TeF_4 units form a chain, similar to the arrangement in pure TeF_4, but with different bridging geometry [138]. The tetragonal pyramids of $O{=}Os(OTeF_5)_4$ are bonded to this chain by fluoride bridges. The central osmium atom is sheltered by the large $OTeF_5$ ligands, and the single remaining coordination site is occupied by the bridging fluorine atom (from [115]).

The principle of electronegative ligands can be extended to polydentate ligands. Recently, *cis*- and *trans*-$(HO)_2TeF_4$ have been reported[15, 132], and the first derivatives, including a xenon compound, are available. *trans*-$(FO)_2SeF_4$ was described as early as 1970[133], while *sym*-$(HO)_3TeF_3$ could actually function as a tridentate ligand[16].

The replacement of oxygen by nitrogen, as in $H_2N{-}SF_5$[133] and $H_2N{-}TeF_5$[134], opens up new prospects, especially for double-bonded $Y{=}N{-}XF_5$ systems. A bidentate nitrogen ligand occurs in *cis*-$[(CH_3)_3SiNH]_2TeF_4$, although the compound is explosive[136]. Taking the analogy a stage further, we arrive at the recently discovered CH_3SF_5[137]. The selenium and tellurium analogues have still not been synthesized. The promising chemistry of all these compounds is still very much in its early stages.

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$$As(OTeF_5)_3 + Xe(OTeF_5)_2 \rightarrow As(OTeF_5)_5 + Xe.$$

D. Lentz, K. Seppelt, *Z. Anorg. Allg. Chem.*, in press.
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$$SbF_5 + 5/3\,B(OTeF_5)_3 \rightarrow Sb(OTeF_5)_5 + 5/3\,BF_3$$

in the absence of solvent: Colorless, hydrolysis-sensitivite solid, M.p = 39 °C, b.p = 67 °C/0.1 mbar. Identified by MS (M^+), Raman spectra, F analysis, and ^{19}F-NMR: $\delta_A = 41.6$, $\delta_B = 35.8$, $J(AB) = 186$ Hz.
$Sb(OTeF_5)_5$ was originally analyzed as $Sb(OTeF_5)_3$ [79]; it is formed by the reaction

$$SbF_5 + 5/3\ B(OTeF_5)_3 \rightarrow Sb(OTeF_5)_5 + 5/3\ BF_3.$$

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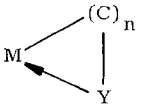
Organometallic Intramolecular π-Olefin-Metal Coordination Compounds

By Iwao Omae*

In this review article complexes of the type X_nM—R are dealt with in which a σ-bonded organic ligand R is additionally linked by a π-bond with the metal M. In other words, the complexes contain metallacycles with three and a half, four and a half, five and a half members, *etc.* Well-known five and a half membered ring systems are those with 4-pentenyl, 1,4-pentadienyl, norbornyl, norbornenyl, cyclooctenyl, and *endo*-dicyclopentadienyl ligands. Metallacycles of this size are strain-free and stable. Donor ligands such as amines and phosphanes can displace the coordinated double bond of the π-ligand from the metal. This C=C double bond is lengthened from *ca.* 133 pm to 136—146 pm by the coordination.

1. Introduction

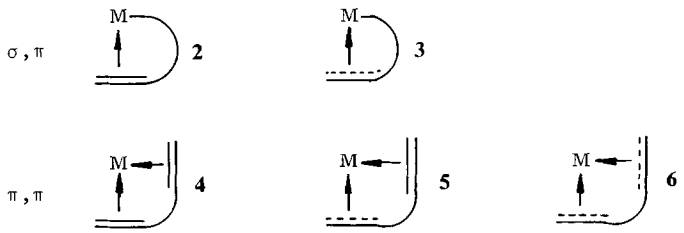
In 1955, *Bähr* and *Müller*[1] defined organometallic intramolecular coordination compounds as compounds of type **1**, in which $n = 3$ or 4. Later, the syntheses of several analogous compounds with $n = 1$, 2, 5 *etc.* were described in the literature, and the author[2-6c] proposed a further classification of such compounds with respect to the donor ligand Y, namely[2-5]: compounds with (i) oxygen ligands (carbonyl, alkoxy, phenoxy groups *etc.*); (ii) nitrogen ligands (amino groups *etc.*); (iii) ligands with multiple bonds (alkenyl, cyclopentadienyl, phenyl groups *etc.*); (iv) other ligands (with halogen, sulfur, phosphorus *etc.*).



1, M = Metall
Y = Donorligand
$n \geq 1$

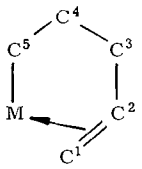
In this review article intramolecular coordination compounds with σ-metal bonded donor ligands Y are tentatively designated as "σ-coordination compounds" (examples of ligands: carbonyl, amino, halogen *etc.*), while analogues with π-metal bonded donor ligands are designated as "π-coordination compounds" (examples of ligands: alkenyl, cyclopentadienyl, and phenyl groups).

The σ-coordination compounds mainly contain elements of the 5th and 6th main groups, usually N, P, As, O or S, as donor atoms, and they tend to form five-membered ring structures, particularly if the donor atom, like nitrogen or sulfur, has no d-electron in the ground state[2-6a,c,d]. Almost all σ-coordination compounds also contain an authentic M—C single bond (for exceptions see [6a]). The π-coordination compounds may be classified into the five groups **2**—**6**. This review deals only with compounds of type **2**, *i.e.* with π-coordination compounds containing a M—C σ-bond. It will be demonstrated that organometallic compounds with intramolecular π-olefin-metal coordination mainly form five and a half membered rings, but in exceptional cases also four and a half and three and a half membered rings, as well as other rings. In addition, the classification, synthesis, reactivity and reaction mechanisms of these metallacycles are discussed.



2. Compounds with Five and a Half Membered Rings

Intramolecular σ-coordination compounds tend to form five-membered rings, while π-coordination compounds, especially those of type **2**, tend to form rings of similar size but with $n + 0.5$ members (n = integer). Thus, *e.g.*, a compound of type **7**[*] contains an almost strain-free five and a half membered ring. The C-atoms can be singly or doubly bonded to each other and also to parts of ring systems.



7

2.1. 4-Pentenyl Compounds

η^3-Allylcobalt complexes readily form the five and a half membered π-coordination compounds **8** by insertion of fluoroolefins into the η^3-allyl-cobalt bond[7,8].

The observation that η^3-allyl(tricarbonyl)cobalt complexes already react at room temperature, whereas the phosphane- and phosphite-complexes react only on heating is explained by the electrophilicity of cobalt being lowered on bonding to the phosphorus ligand. Monophosphane- and monophosphite-substituted products **8** can

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[*] The C-atoms of the ligands in **7**—**9**, **93**, **100**—**103** and in Figure 1 are not numbered systematically.

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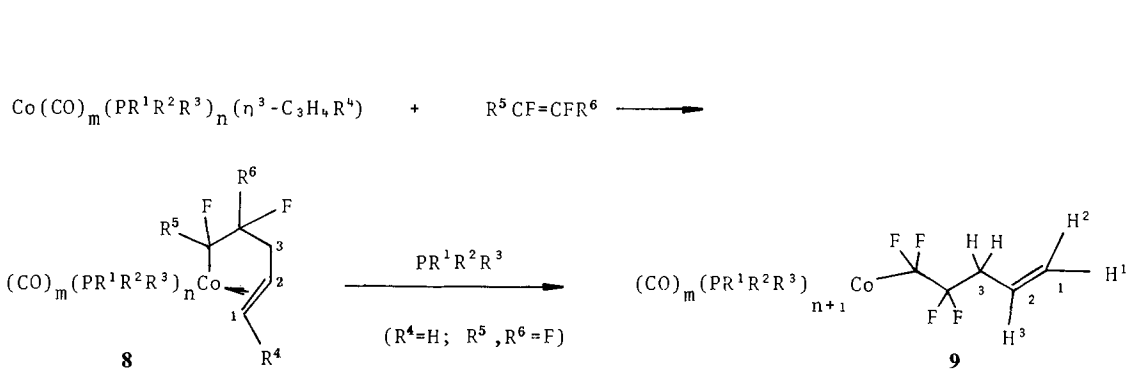


R^1–R^3 = Me, Ph, OMe; R^4 = H, Ph, Me; R^5, R^6 = F, CF_3; n + m = 3; **8a**, R^1–R^3 = Me; R^4 = H; R^5, R^6 = CF_3; n = 1

react with further donor ligands with ring-opening to give **9** (dectected, *inter alia*, by ^{1}H- and ^{13}C-NMR).

Figure 1 shows the structure of the product **8a** formed on reaction of octafluoro-2-butene with η^3-allyldicarbonyl(trimethylphosphite)cobalt[7]. The Co—C^1 and Co—C^2 bond lengths in this trigonal-bipyramidal structure are almost identical, hence the terminal double bond is olefinically bonded. The pentenyl chain forms the characteristic five and a half membered ring structure incorporating the central metal.

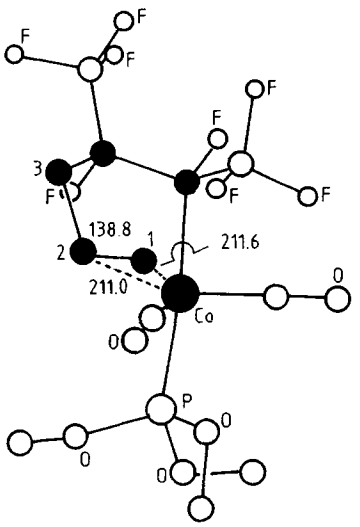


Fig. 1. Structure of **8a** in the crystal. Bond lengths in pm [7].

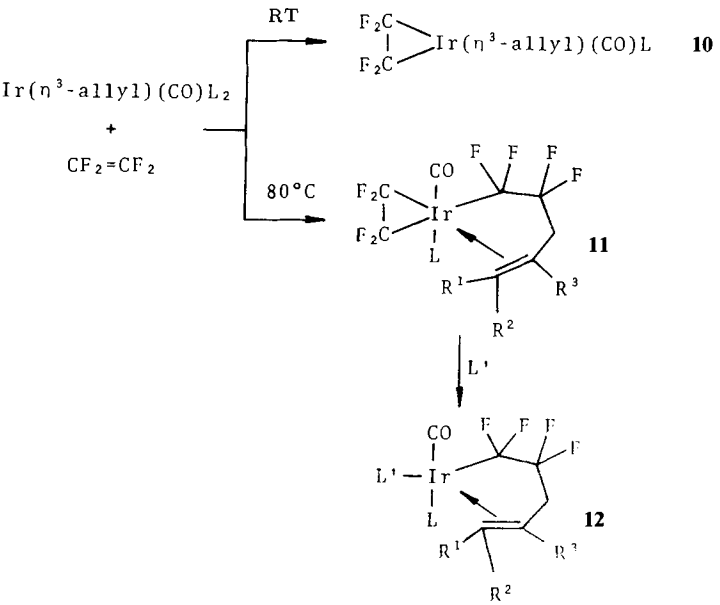
Triphenylphosphane- and triphenylarsane-substituted η^3-allylcarbonyliridium complexes also exhibit low activity towards tetrafluoroethylene. At room temperature, only one ligand is exchanged to give the complex **10**; on heating, however, the insertion products **11** are formed. The coordinated tetrafluoroethylene can subsequently be readily replaced by carbon monoxide or triphenylphosphane to give the substituted product **12** without ring-opening taking place[9].

Interactions between main-group metal atoms and CC double bonds have been investigated by *Oliver et al.*[10-16a] on compounds **13** bearing terminal olefins:

$M-(CH_2)_n-CH=CH_2$, M = Al [10, 11], Zn [10, 12, 13], $n = 2-4$

13

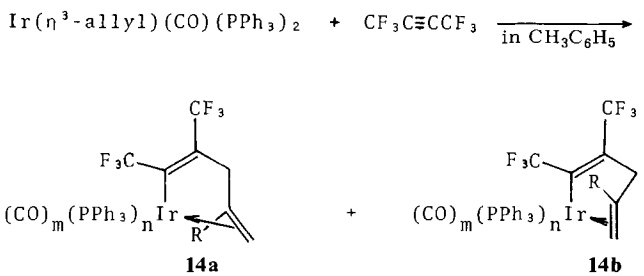
It was demonstrated that only 4-pentenyl compounds ($n = 3$) have a ring structure (NMR results). Such five and a half membered ring systems having the 4-pentenyl skeleton have also been prepared by reaction of ω-olefinic Grignard reagents with η^5-cyclopentadienyl derivatives[16b,c] and *via* other routes[16d,e].



η^3-allyl = 1-MeC_3H_4, 2-MeC_3H_4; L = PPh_3, $AsPh_3$; L' = PPh_3, CO; R^1–R^3 = H, Me

2.2. 1,4-Pentadienyl Compounds

Like olefins, acetylenes also react with η^3-allyliridium complexes to give *cis*-inserted diene compounds **14a** and **14b**, along with polymerization products of the acetylenes and small amounts of the open-chain *trans*-insertion products **15**[17].

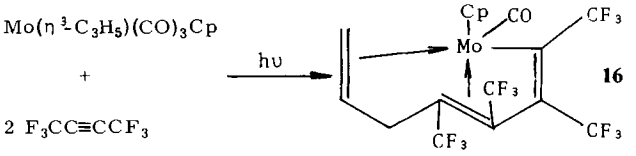


14a **14b**

$Ir[(CF_3)C\overset{I}{=}C(CF_3)-CH_2-CHR=CH_2](CO)(PPh_3)_2$ **15**

η^3-allyl = C_3H_5, 2-MeC_3H_4;
R = H, Me;
m, n = 1,2; m + n = 3

Products analogous to **14** are also accessible photochemically from η^1-allylcarbonyl-iron[18] or -cobalt complexes[18b] and, *e.g.*, hexafluoro-2-butyne. A corresponding molybdenum complex substrate, however, afforded the bis-insertion product **16**.



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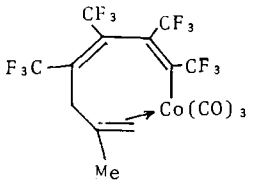


17 Cp = (η^5-C_5H_5)

Double insertion of the fluoroalkyne into tricarbonyl-η^3-methylallylcobalt, on the other hand, leads to formation of the metallacycle **17** with a seven and a half membered ring structure (in low yields together with polymers)[8].

2.3. Norbornyl and Norbornenyl Compounds

Numerous η^3-allyl complexes **18** react with cyclic olefins, *e.g.* norbornene, norbornadiene and their derivatives, and bicyclo[2.2.2]octene, to give a variety of insertion products (**19–26**), all of which contain five and a half membered rings[19–22].

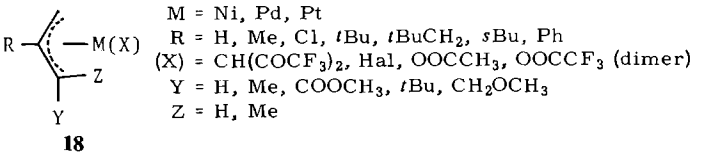
η^3-Allylnickel complexes **18**, *e.g.*, react under mild conditions with norbornene, presumably *via* initial formation of ordinary π-complexes, which then react with sodium acetate[23] or potassium acetate[24] to give the acetato-bridged nickel compounds **19**. The bond lengths in these norbornyl and norbornenyl complexes are indicative of a pronounced "*trans*-effect"[22,25–29].

2.4. Cyclooctenyl Compounds

In 1957, *Chatt et al.* synthesized 1,5-cyclooctadieneplatinum(II) chloride **27a**[30,31], and *Schultz* prepared the dinuclear methoxy derivative **28a**[32]. **27a** can be prepared from 1,5-cyclooctadiene and Na_2PtCl_4, while **28a** can be obtained by methanolysis of **27a** in the presence of anhydrous sodium carbonate. Reactions of 1,5-cyclooctadiene complexes **27** with other alcohols[33], sodium methoxide[34], water[35], silver acetate[36], malonates[37], acetoacetates[37,38], and thallium β-dionates[39,40], analogously lead to compounds of type **28** to **36**. Complexes with amines have so far evaded isolation[41].

Hydride addition to tetracarbonyl-1,5-cyclooctadienemanganese(I) with $NaBH_4$ leads, *via* hydrogenation of one of the two CC double bonds of the educt, to formation of the metallacycle **37**. Reaction of the cation with sodium methoxide or sodium azide, respectively, affords methyl ethers or azides **38**[42].

Bis(1,5-cyclooctadiene)metals react with cyclopentadiene (or methylcyclopentadiene[43]) or acetylacetone[44]



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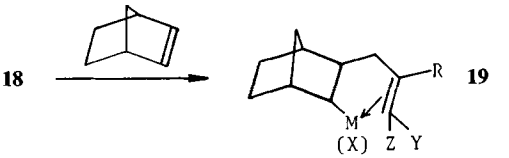

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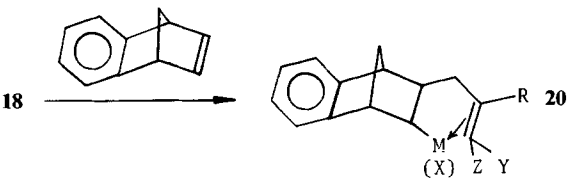

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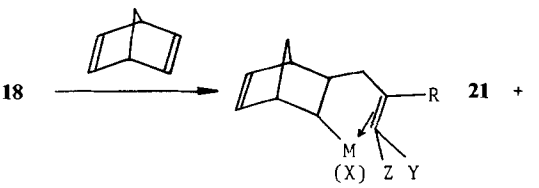

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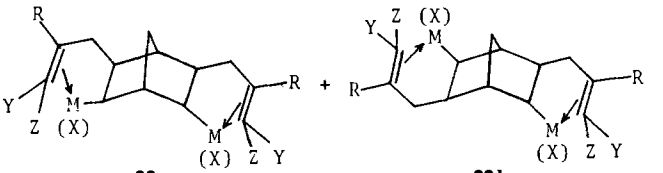
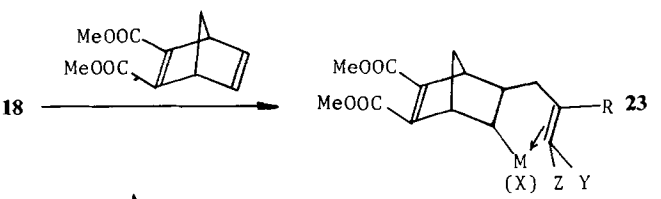


22a **22b**



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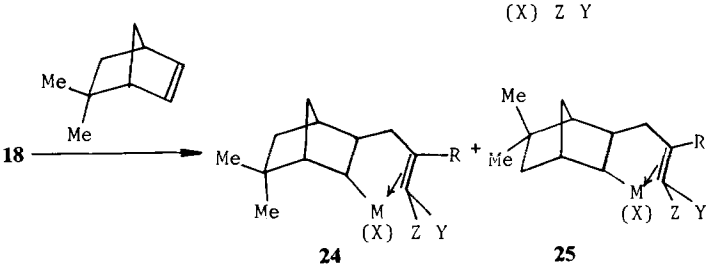
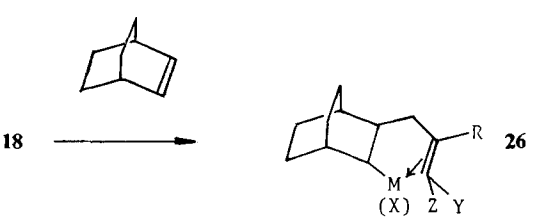
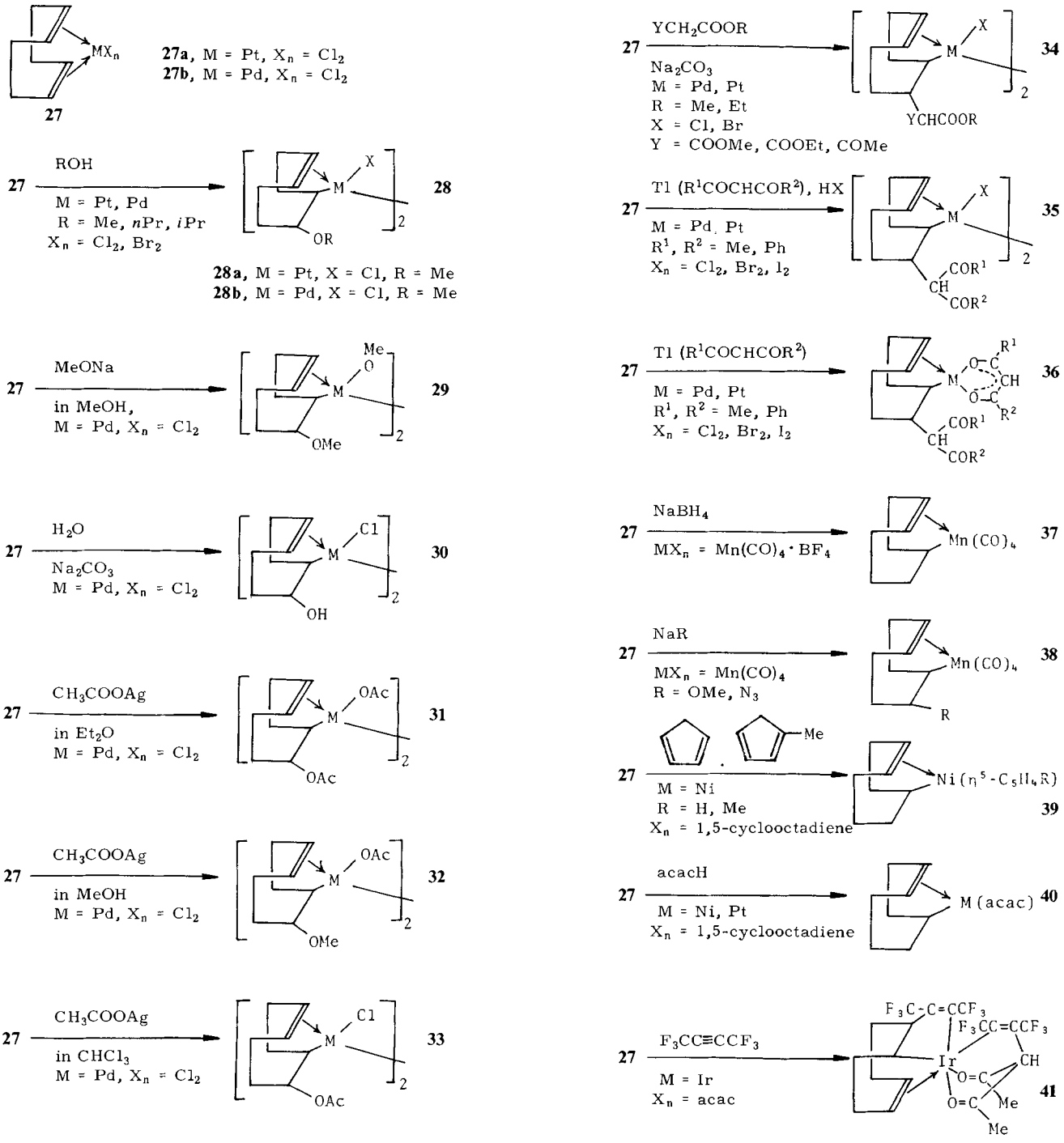


24 **25**



26

with exchange of one of the two ligands to give the complexes **39** and **40**, respectively. In **40** the coordination of the nickel is essentially square planar, and the length of the



CC double bond is surprisingly large (142 pm) even though it is 7 pm shorter than any other CC bond in the ring[44a].

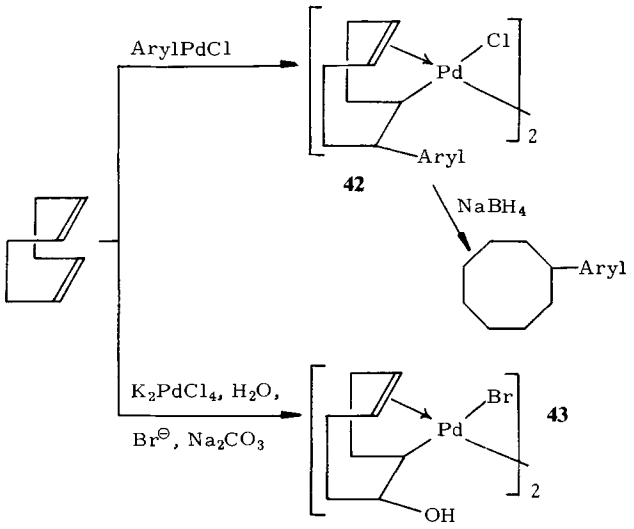
On reaction of 1,5-cyclooctadieneiridium acetylacetonate with hexafluoro-2-butyne the alkyne adds to both ligands to give the addition product **41** (X-ray structure analysis)[45].

Arylpalladium chlorides react directly with 1,5-cyclooctadienes, *i.e.* with circumvention of the monomeric 1,5-cyclooctadiene step, to give the dinuclear cyclooctenyl complexes **42**, which can be readily reduced to arylcyclooctanes[46]. K_2PdCl_4 likewise reacts directly with 1,5-cyclooctadiene and bromide ions to give **43**[47].

The stable dimer **44** is formed from *Z-cis*-bicyclo[5.1.0]octa-3-ene and bis(benzonitrile)dichloropalladium by transfer of chlorine from the palladium to the ligand[48].

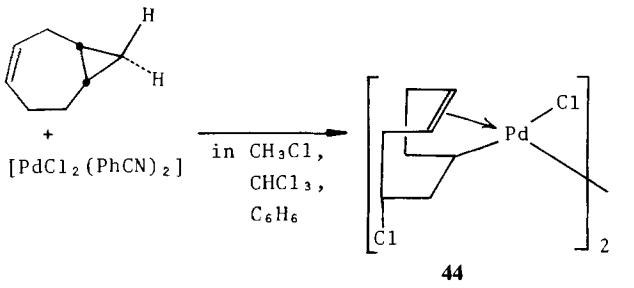
Halogen-bridged cyclooctenyl complexes of type **45** (examples: **28**, **30**, **33**—**35**, **43**) react with various kinds of donor ligands such as amines, phosphanes, phosphites and arsanes with cleavage of the halogen bridges to give the mononuclear complexes **46**[30,31,41,49–51].

The dimers **45** are also cleaved to the corresponding monomers on reaction with carbon monoxide. In the case of **45**, where Y = OR, the unstable carbonyl derivative **47** is first formed, which immediately reacts further with alcohols to give alkoxycarbonyl compounds **49**. Nucleophilic attack of the alcohol at the carbonyl group and subsequent

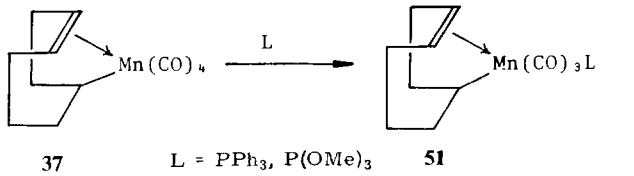


Aryl = C_6H_5, p-MeC_6H_4, p-$MeOC_6H_4$

cleavage of the alkoxy group Y leads to formation of the second coordinated CC double bond[33a,52].

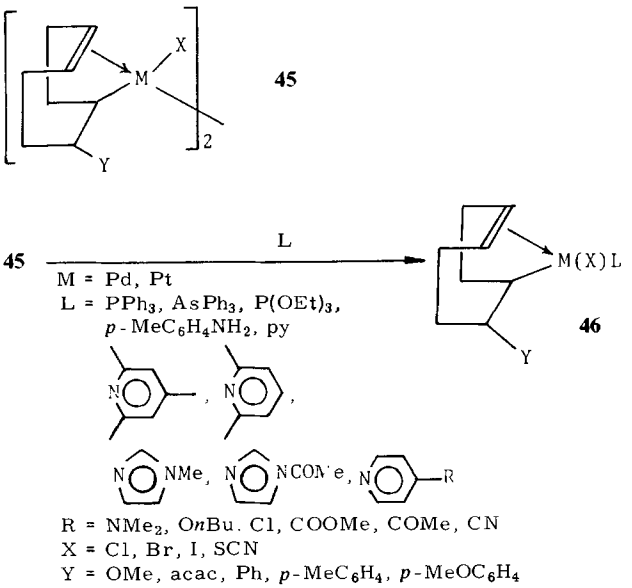


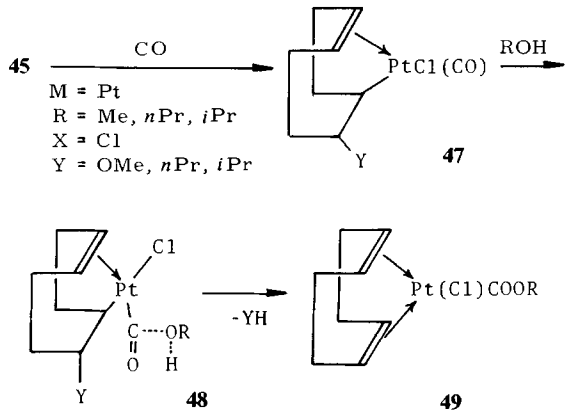
Thallium cyclopentadienide[47,53], 2,2,6,6-tetramethyl-3,5-heptanedionatothallium[47], and even ethylenediamine[54] likewise react with **45** with rupture of the halogen-bridge to give **50**. In contrast, in the case of **37** a simple ligand exchange takes place with donor ligands[42].

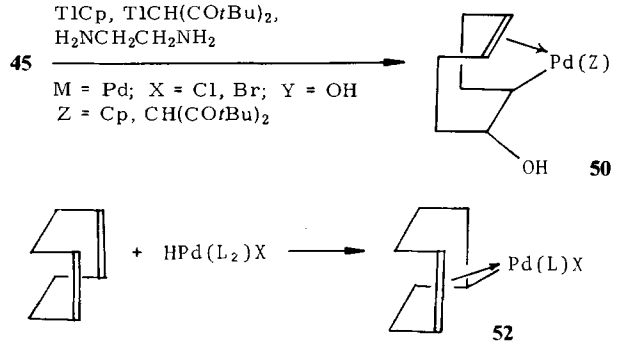


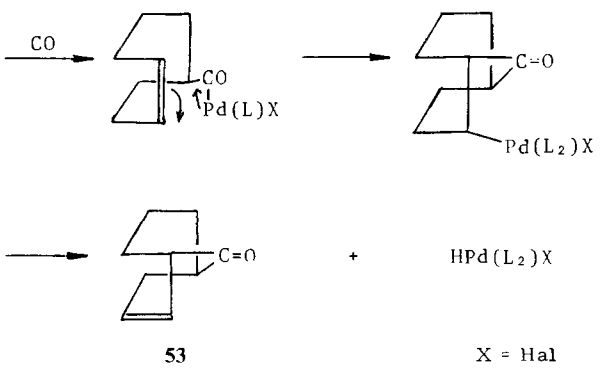
Brewis and *Hughes* were able to prepare bicyclo[3.3.1]non-2-en-9-one **53** by reaction of 1,5-cyclooctadiene with carbon monoxide in the presence of 1% diiodobis(triphenylphosphane)palladium(II) (150 °C, 1000 bar)[55]. Formation of the transannular addition product **53** suggested a reaction route involving formation of **52** with subsequent carbonyl insertion.

Methanolysis of dinuclear 2-methoxycyclooctenylpalladium complexes, *e.g.* of type **28** and **29**, leads to a broad spectrum of products (see [32,34]), while carbonylation of the analogous hydroxy derivative **30** yields exclusively the β-lactome, *trans*-(*Z*)-4-cyclooctene-1,8-carbolactone[35,56]. Basic methanolysis and methylation lead to the *trans*-(*Z*)-





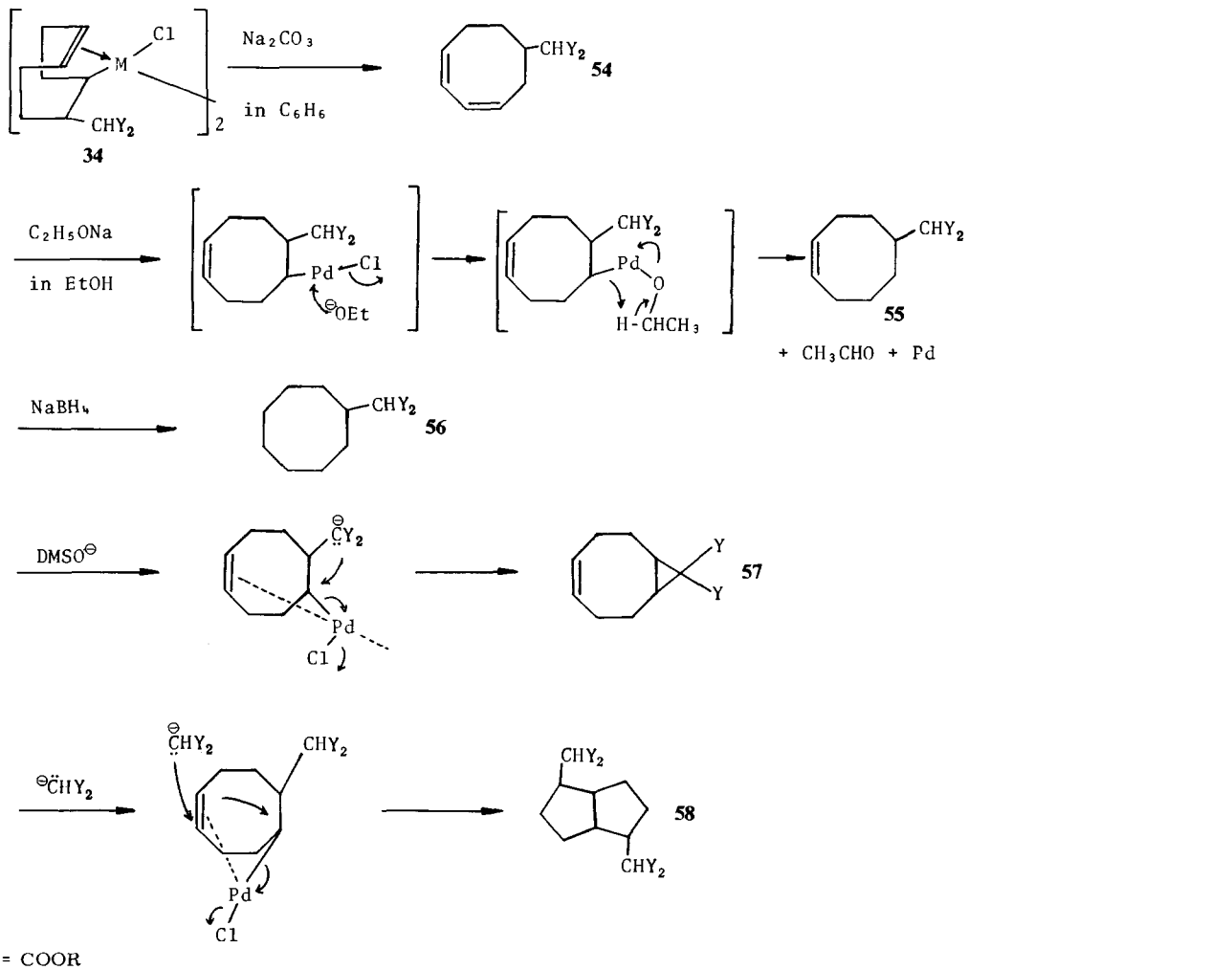




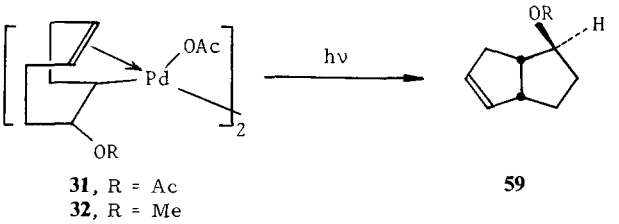
methoxy ester[57]. Thermolysis of **30** in acetone leads to formation of the γ,δ-unsaturated ketone, 4-cyclooctenone; this is the product expected from the Wacker oxidation of 1,5-cyclooctadiene, a reaction which has been demonstrated to proceed *via* a σ-bonded β-hydroxyalkylpalladium intermediate[58].

On heating under reflux with bases such as triethylamine or anhydrous sodium carbonate, the malonate-substituted cyclooctenyl complexes **34**[37,38] undergo cleavage, yielding the 3,5-cyclooctadienylmalonates **54**. On the other hand, treatment with sodium ethoxide leads to reductive cleavage of the Pd—C σ-bond to give the diethyl 4-cyclooctenylmalonate **55**.

Reduction of **34** with $NaBH_4$ in ether yields cyclooctyl malonates **56**. In contrast, stronger bases should abstract the activated hydrogen atom of the malonate group. Thus, **34** reacts with the dimethyl sulfoxide (DMSO) anion at room temperature to give bicyclo[6.1.0]non-4-ene-9,9-dicarboxylates **57**. Reaction of **34** with malonate leads in a transannular reaction to formation of bicyclo[3.3.0]octane-2,6-dimalonates **58**[37,38].



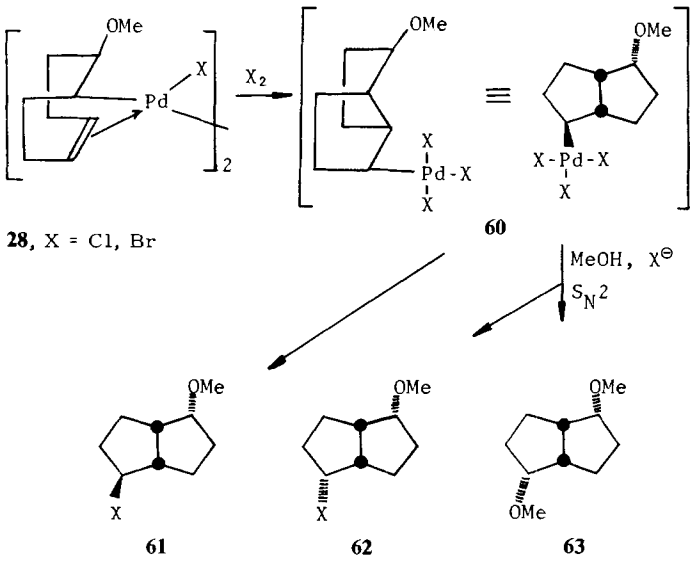
Photolysis of **31** likewise yields transannular reaction products; in addition to 55% of **59** also 10% of the saturated bicycle is formed. The methoxy compound **32** behaves similarly[59].



Halogenation of the complexes **28** leads to formation of the bicycles **61**—**63**. For the mechanism of this reaction *Wong* and *Stille*[60] proposed an oxidative addition *via* **60** with subsequent reductive elimination (for protonation and other reactions of cyclooctenyl complexes see [61]).

2.5. *endo*-Dicyclopentadiene Compounds

In 1908 *Hofmann* and *Narbutt*[62] prepared the first intramolecular coordinated dicyclopentadiene complex **65a** by direct reaction of *endo*-dicyclopentadiene with K_2PtCl_4 in aqueous methanol, and thus succeeded in circumventing the devious route *via* the diolefin complex **64**. However, they did not mention anything regarding intramolecular coordination. In 1957, *Chatt et al.* prepared the same compound from **64** and proposed that it has a structure with intramolecular coordination[30,31]. Later, in 1966, *Whitla et*

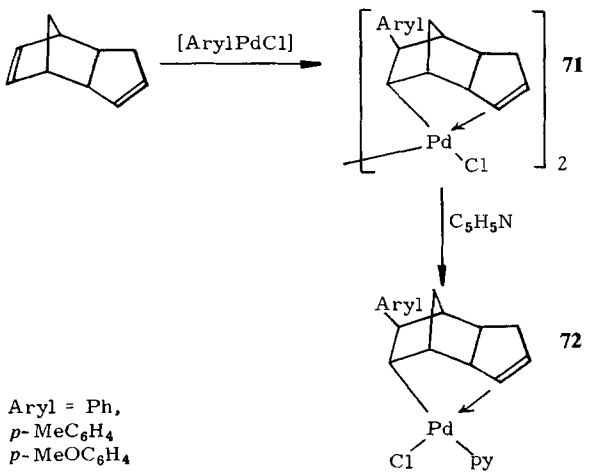


28, X = Cl, Br

61 **62** **63**

al. demonstrated by an X-ray structure analysis that the compound exhibits a very strong *trans*-effect (see Fig. 2)[63].

Numerous complexes with intramolecular coordination have been synthesized from **64**, *e.g.* complexes of type **65**—**70**[64-67].



Aryl = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$

In contrast, analogues of **69** and **70** with aromatic substituents on the ring are directly accessible from arylpalladium chloride and *endo*-dicyclopentadiene. On treatment with pyridine, **71** affords the pyridine-substituted monomer **72** without scission of the intramolecular σ,π-coordination[46].

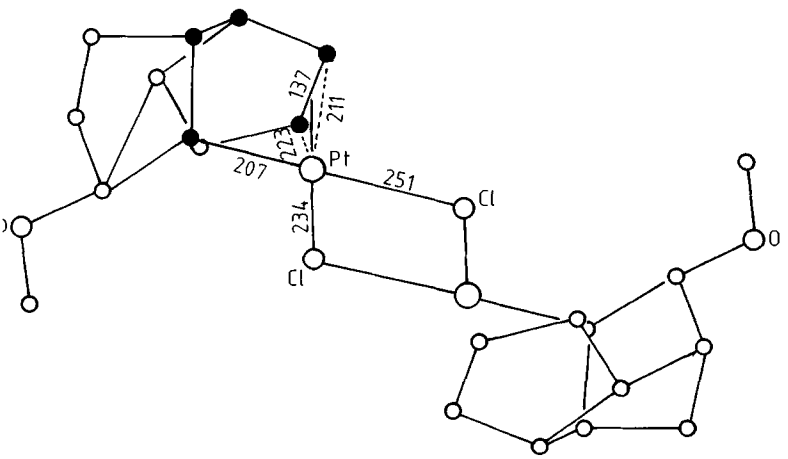
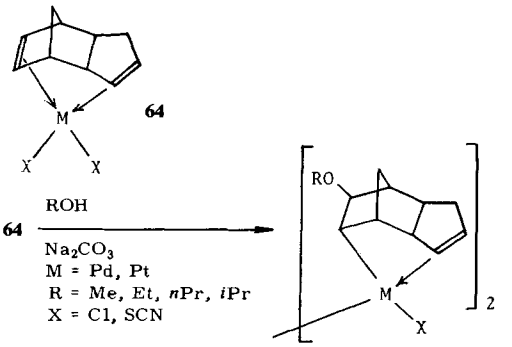
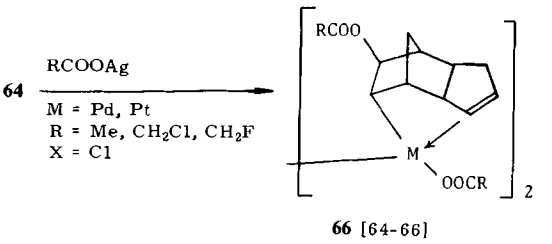


Fig. 2. Structure of **65a** in the crystal. Bond lengths in pm [63].

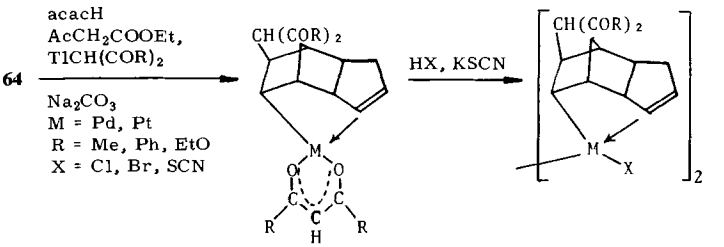


65

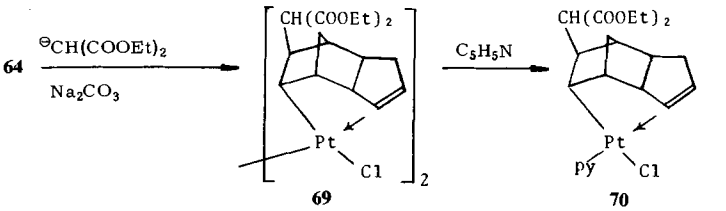
65a, M = Pt, R = Me, X = Cl



66 [64-66]



67 [40,67] **68**

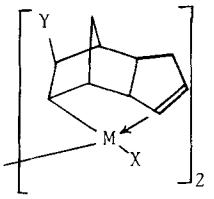


69 **70**

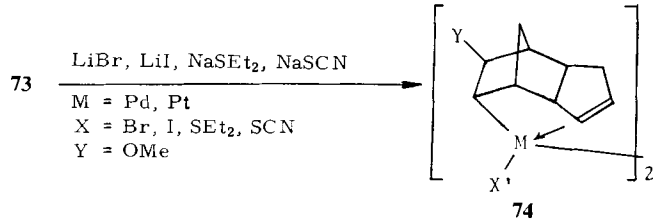
The bridged dimers **73** can generally undergo bridge-exchange reactions to give the products **74** on reaction with, *e.g.*, bromide, iodide, ethanethiolate or thiocyanate ions[30,31]. Amines, phosphanes, and isocyanates, on the other hand, induce cleavage of the bridge with formation of mononuclear complexes **75**[30,31,53,68-71].

Reaction of chloro-bridged **73** with the hyperoxide ion O_2^- leads to formation of the novel dioxygen complex **76**[72]. The fairly labile dioxygen bridge, however, is readily replaced by chlorine on warming in CH_2Cl_2, *i.e.* the starting compound **73** is obtained again, in quantitative yield. Treatment of **76** with methanol at room temperature leads to formation of the methoxo-bridged complex and hydrogen peroxide.

Reaction of **73** with cyclohexyl isocyanide initially yields the monomer, which after olefin displacement and

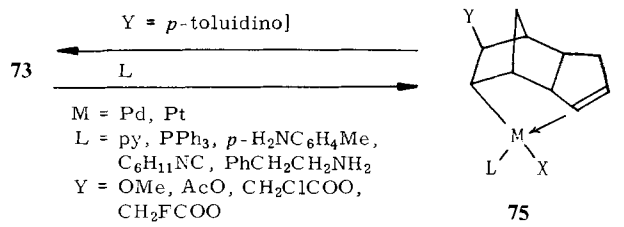


73, X = Cl, SCN



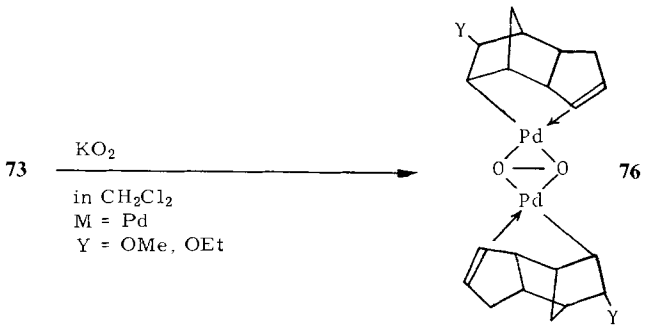
73 → **74**: LiBr, LiI, $NaSEt_2$, NaSCN; M = Pd, Pt; X = Br, I, SEt_2, SCN; Y = OMe

74



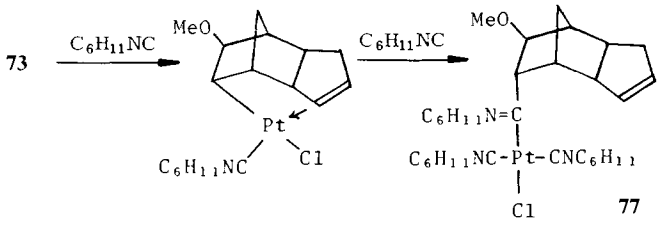
73 ⇄ **75**: KI [M = Pt, X = Cl, Y = *p*-toluidino]; L; M = Pd, Pt; L = py, PPh_3, *p*-$H_2NC_6H_4Me$, $C_6H_{11}NC$, $PhCH_2CH_2NH_2$; Y = OMe, AcO, CH_2ClCOO, CH_2FCOO

75



73 → **76**: KO_2; in CH_2Cl_2; M = Pd; Y = OMe, OEt

76

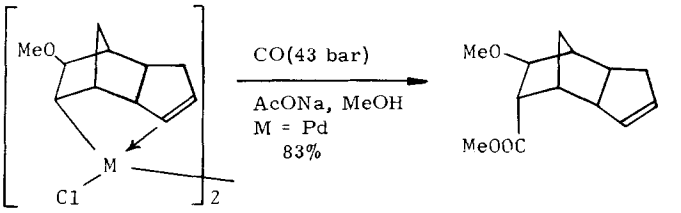


73 → **77**: $C_6H_{11}NC$; $C_6H_{11}NC$

77

subsequent isocyanide insertion into the Pt—C σ-bond affords the *trans*-complex **77**[69] (cf. [73]).

73, M = Pt, readily undergoes carbonylation under mild conditions to give intramolecular coordinated species of type **75** (L = CO), whereas high-pressure carbonylation of **73**, M = Pd, leads to the metal-free esters **78**[57].



73 → **78**: CO(43 bar); AcONa, MeOH; M = Pd; 83%

73

78

Triphenylphosphane-substituted platinum complexes **79** react with carbon monoxide to give the carbonyl derivatives **80**[74]. In the case of **79**, M = Pd, the complex **80** cannot be isolated; however, it can be converted into the corresponding ketones **81a** or the aldehyde **81b**[75].

2.6. Cyclooctatriene-Dimetal Compounds

In 1963, *King* synthesized the compound $C_8H_{10}Fe_2(CO)_6$ by reaction of 1,3,5-cyclooctatriene with $Fe_3(CO)_{12}$ and suggested that it had the structure **82**[76]. Shortly afterwards, *Emerson et al.* concluded from a Mössbauer study that it has the structure **83** in the solid state[77]. However, in

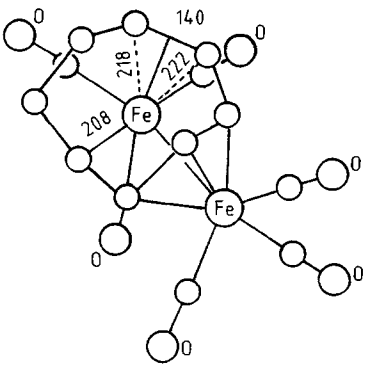
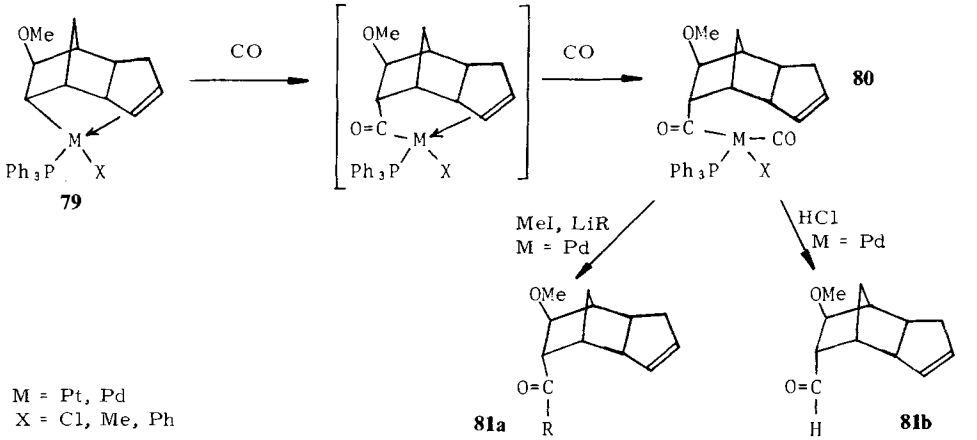


Fig. 3. Structure of **84** in the crystal. Bond lengths in pm [78].



79 → **80**: CO; CO

80 → **81a**: MeI, LiR; M = Pd

80 → **81b**: HCl; M = Pd

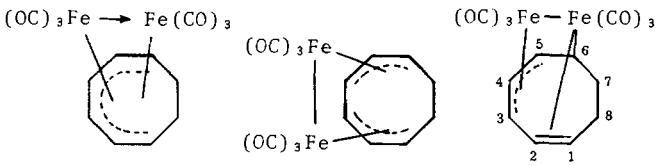
M = Pt, Pd
X = Cl, Me, Ph

81a

81b

1969 *Cotton* and *Edwards* carried out a three-dimensional X-ray crystallographic analysis on the compound and found that it has the unsymmetric structure **84** in the solid state[78]: The molecule does not have a plane of symmetry and the metal atoms are not structurally equivalent, one $Fe(CO)_3$ group being bonded allylically to C^3, C^4, and C^5, while the other coordinates the olefinic double bond and is coupled with C^6 by a single bond (Fig. 3)[78].

Dinuclear carbonyl compounds of similar structure are not only found with iron[78-86], but also with ruthenium[87-89] and rhodium[90]. The skeletal structure found in **84** also appears in *o*-annelated cyclooctatrienes (three-membered[84,85], four-membered[79,80], six-membered (benzene) rings[86], and other rings[88]).



82 **83** **84**

Cotton et al.[83] found by ^{13}C-NMR spectroscopic investigations that the molecular structure of **84** is markedly fluxional in solution. At temperatures below −65 °C, the ^{13}C-NMR spectrum is in complete accord with the skew structure observed in the solid state (Fig. 3). The first changes in the spectrum—observed between −65 and about 8 °C—result from a "twitching process" in which the two enantiomeric forms of the molecule interconvert by minimal movement of the $Fe_2(CO)_6$ moiety. At the same time a rapid scrambling of the CO-groups of the η^3-allyl-bonded $Fe(CO)_3$ moiety takes place. Above 8 °C, scrambling of the CO groups on the other iron atom commences.

The "twitching process".

2.7. Other Complexes with Five and a Half Membered Rings

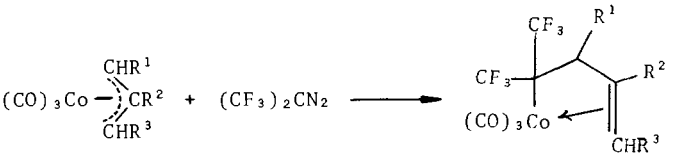
Of the acid chlorides $CH_2{=}CH{-}(CH_2)_n{-}COCl$ having a double bond at the terminal position, only 4-pentenyl chloride ($n=2$) reacts with $NaCo(CO)_4$[91a]. The stability of the five and a half membered ring structure is also apparent in some complexes which contain several CC double bonds and in which metal coordination to rings of other size would be possible[91b,c]. Further examples of compounds of this type are to be found in refs.[92-106].

3. Compounds with Four and a Half Membered Rings

These metallacycles, which are generally less stable than the five and a half membered analogues, are mainly obtained by insertion of alkynes; they are also accessible from norbornadiene-metal dihalides (cf. Sections 2.4 and 2.5).

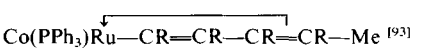
3.1. 3-Butenyl and 1,3-Butadienyl Compounds

Olefins readily insert into allylic bonds of complexes, mainly giving five and a half-membered π-coordination compounds (see Section 2). Correspondingly, the insertion of a C_1-moiety (from hexafluoro-2-diazopropane) leads to four and a half membered metallacycles such as the extremely air-sensitive cobalt compounds **85**[107].

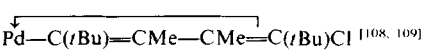


R^1 - R^3 = H, Me **85**

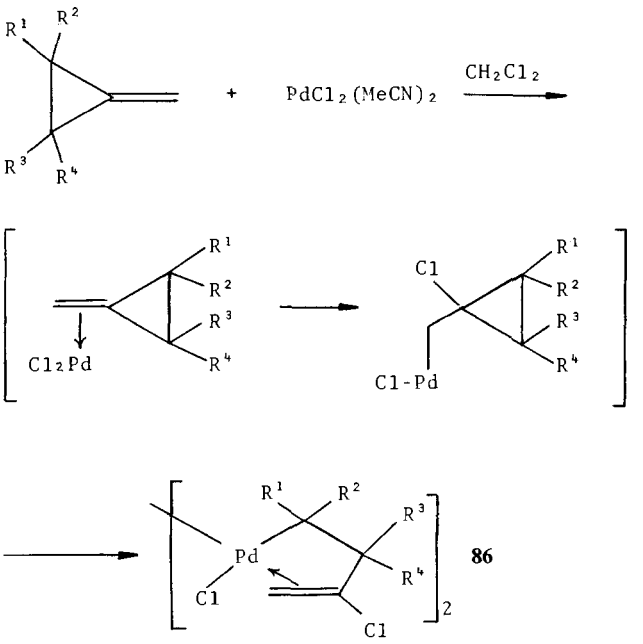
Alkynes likewise tend to insert into M—C, M—Hal and M—H bonds. Examples of this are the insertion of two molecules of RC≡CR (R = CF_3, COOMe) into the Ru—C σ-bond of $RuMe(PPh_3)_2Cp$, leading to the four and a half membered metallacycle



Analogously, $Pd(Cl)_2(PhCN)_2$ and *t*BuC≡CMe ("chloropalladation") afford complexes with the partial structure

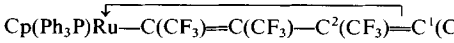


Here, the insertion takes place into the M—Cl bond. If the $Pd(Cl)_2(PhCN)_2$ is allowed to react simultaneously with the alkyne PhC≡CR (R = mesityl) and the olefin $CH_2{=}CH(t\text{Bu})$ the mixed end product is formed[110].



R^1 - R^4 = H, D, COOMe, Ph

Equivalent insertions into M—H bonds are also possible. Reaction of $RuH(PPh_3)_2Cp$ and hexafluoro-2-butyne, *e.g.*, leads not only to formation of the bis-insertion product with a four and a half membered ring

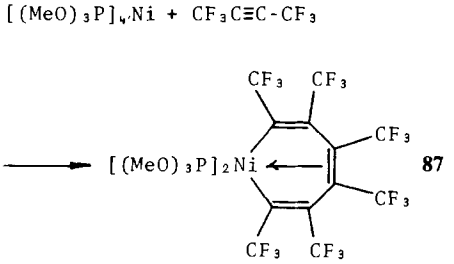


but also of the acyclic mono-insertion product[111,112].

Methylenecyclopropane reacts with chloropalladium complexes with ring opening to give the dimer **86**[113-115].

A ruthenium complex with a four and a half membered ring structure is surprisingly formed by insertion of the alkyne into a Ru—H bond and not into the Ru—C bond[111,112,116].

As example of a cyclometalated alkyne trimer we have the complex **87**, which contains two four and a half membered rings[117]. Interestingly, pyrolysis of the cyclohexylphosphane analog of **87** yields hexakis(trifluoromethyl)benzene[118]. Ring-opening and other reactions of the 3-butenyl and 3-butadienyl compounds have been reported elsewhere[119-122].



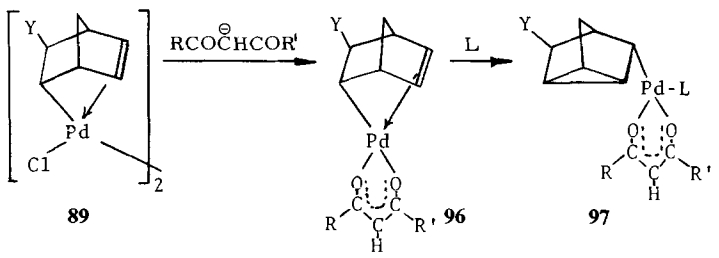
3.2. Norbornenyl Compounds

Norbornadiene-metal dihalides **88** similarly provide general access to intramolecular coordination compounds such as the cyclodiene-metal dihalides **27** and **64**.

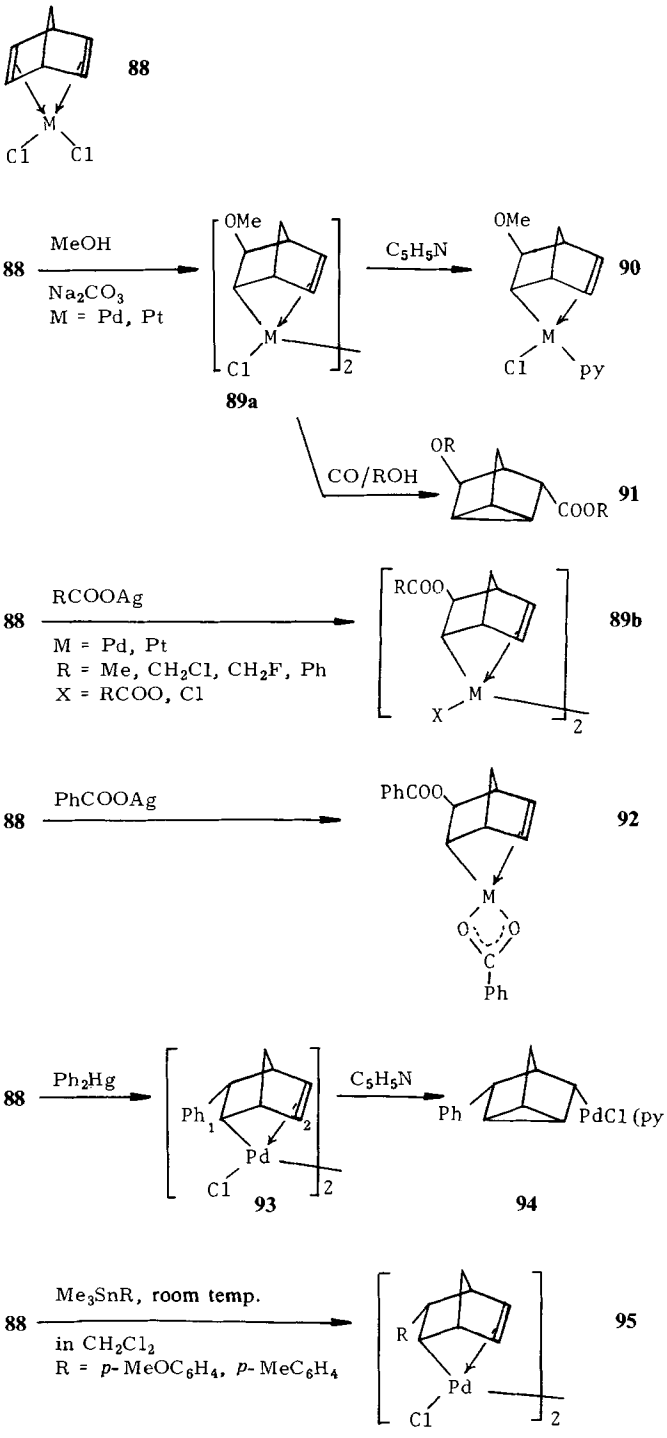
Thus, pyridine-substituted four and a half membered mononuclear complexes **90**[71] are obtainable from **88** *via* the dimeric methoxy-derivatives **89a**[53,57,123]; the same bridge-splitting occurs during carbonylation of **89a** (in methanol) to give the nortricyclane derivative **91**[124,57]. Reaction with silver carboxylate gives in most cases the species **89b** with carboxylato-bridges together with chloro-bridged $[AcOC_7H_8PdCl]_2$ and Pd- or Pt-carboxylates such as **92**[64].

Dichloro(norbornadiene)palladium also reacts with diphenylmercury[125,126] or aryltrimethyltin[127] to give the chloro-bridged dinuclear complexes **93** and **95**, respectively, which in contrast to **89a** have an *endo*-structure (X-ray analysis of **93** see [125]).

The dimeric norbornenyl complexes of type **89** react with multidentate ligands to give the cleavage products **96**.



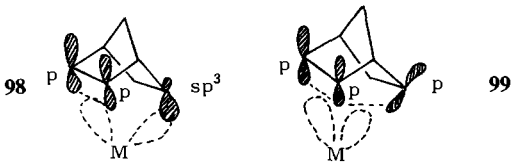
L = py, PPh_3, $PPhMe_2$, $SbPh_3$, $AsPh_3$; R, R' = CF_3, Ph;
Y = OMe, CH_3COO



Reactions of these with neutral donor ligands afford metalated nortricyclane derivatives **97**; reactions with monoolefins or 1,3-dienes lead to analogous derivatives[128] (cf. also [60,73]).

All these norbornenyl complexes contain four and a half membered rings, which can be expected to show relatively high ring strain. In fact the complexes should be unstable, since, according to model considerations, the CC double bond cannot coordinate orthogonally to the central atom. Nevertheless, almost all of these compounds can be prepared and isolated. *Green* and *Hancock* suggested that the π-homoallylic structure **99** is preferred over the four and a half membered metallacyclic form **98**[123]. However,

whether this is so or not has not yet been finally settled[125, 129].

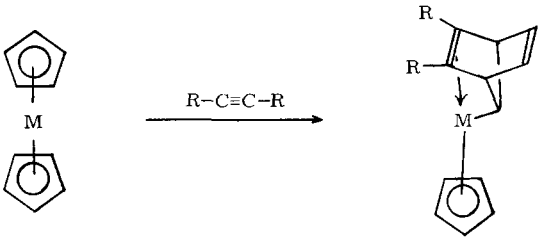


This argument was based on the significant deshielding of the C*H*Pd proton ($\delta = 4.20$) observed in the methoxynorbornenyl complex **89a**; for comparison: in the *endo*-dicyclopentadiene complex **65**, M = Pd, X = Cl, R = Me, the C*H*Pd proton absorbs at $\delta = 3.47$. Also the observation that norbornenyl complexes very readily form nortricyclanes (*e.g.* **91**, **94**, **97**) could serve as an argument in favor of the homoallylic π-coordination.

In this connection, *Hughes* and *Powell* have carried out ^{13}C-NMR spectroscopic investigations on the complexes **100**—**103**[129] (Table 1). They also preferred the π-homoallylic structure for **100**. Their arguments were as follows: J(Pt—C^1) of **100** is distinctly smaller than in the complexes **101**—**103**. This implies that the C^1—Pt bond has more "p-orbital character" than a typical norbornyl-Pt σ-bond. C^2 and C^3 in **100** must differ drastically in their interaction with the metal, for their coupling constants differ by about 160 Hz! Owing to the rigid carbon skeleton in the bicyclic system in **100** the C^2—C^3 axis must tilt away from the perpendicular, with the result that the coordination plane of the metal must intersect the C^2—C^3 axis at a point much closer to C^3 than C^2. Furthermore, the marked upfield shift of C^1 and C^2 in **100** in comparison to the corresponding signals of the enyl complexes **101**—**103** is indicative of more shielding of these two nuclei in **100**. The chemical shift of C^3 is of similar magnitude in all complexes. Aside from these findings in favor of homoallylic π-coordination of type **99** there are, however, a number of contradictory findings.

Segnitz, Bailey and *Maitlis* found that the C^1—C^2 bond length in **93** was 235 pm and considered this to be too long for homoallylic conjugation. They suggested the homoallylic form as being merely a transition state or metastable intermediate on the reaction path from **93** to **94**[125].

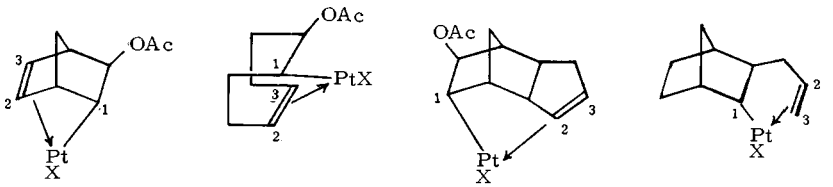
Sandwich compounds such as nickelocene react with alkynes to give the half-sandwich complexes **104**[130–138].



M = Ni, Mo, Pt; R = COOMe, CF_3 **104**

Four and a half membered π-coordination compounds are formed by Diels-Alder reaction of the alkyne with one of the cyclopentadiene rings (for the X-ray structure analysis of **104**, M = Ni, R = COOMe, see [131]). There are metal-ligand bonds not only to the η^5-cyclopentadiene ring, but also to the bridge C-atom (196.4 pm) and to the substituted CC double bond (distance to midpoint 183 pm). At 145.0 pm this ring double bond is significantly longer than a normal olefin bond (133.0 ± 2.1 pm)[131].

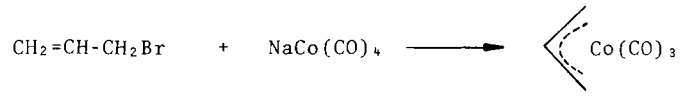
Table 1. ^{13}C-NMR data of the complexes **100**–**103**. X = hexafluoroacetylacetonate.



	100	**101**	**102**	**103**
δ(C^1)	0.3	25.9	32.8	37.4
J(C^1—H) [Hz]	160	145	150	—
J(Pt—C^1) [Hz]	470	730	782	758
δ(C^2)	61.3	77.9	87.9	87.0
J(C^2—H) [Hz]	178	157	170	157
J(Pt—C^2) [Hz]	132	255	250	277
δ(C^3)	79.2	82.2	85.4	56.2
J(C^3—H) [Hz]	181	154	168	159
J(Pt—C^3) [Hz]	296	260	259	305

4. Compounds with Three and a Half Membered Rings

The η^3-allylcobalt complex **105** is readily accessible by reaction of sodium tetracarbonylcobaltate with allyl bromide. Reaction with acryloyl chloride, however, affords the complex **106** with a π-coordinated double bond[91a]. Of the other acryloyl compounds[139–141] special importance attaches to the complex **107**, in which the C^1—C^2 and C^2—C^3 bond lengths are almost equal[142]; the η^3-acryloyl moiety of this complex is thus considered as intermediate between an η^3-allyl system with oxygen atom and an η^2-olefin, η^1-acyl system.



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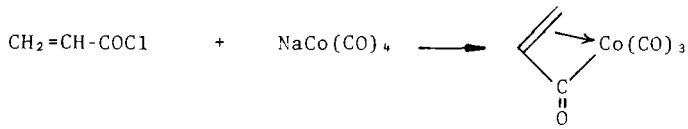
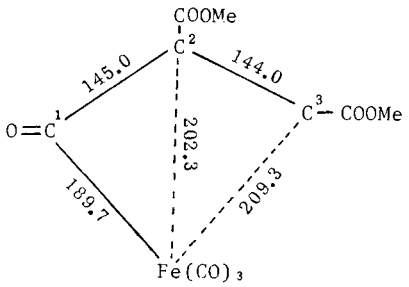


106

Reaction of methallylpalladium chloride with triphenylphosphane affords methallyl(triphenylphosphane)palladium chloride **108**. *Shaw et al.* also described this complex as being an intramolecular coordination compound, on the basis of NMR spectral data[143]. An X-ray structure analysis confirms their view[144]. The π-allyl character of **108** is much less pronounced than that of **107**.



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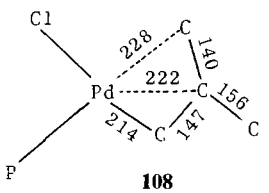


108

Reaction of $Fe_3(CO)_{12}$ with octafluoro-1,3- or -1,4-cyclohexadiene leads to formation of a mononuclear iron complex[145]; an X-ray structure analysis of the complex suggested the presence of a σ,π-bond between metal and ligand and the conformation of the complexed cyclohexadiene shown in Figure 4[146]. Analogous compounds, not only with iron[147-150] but with ruthenium[151], cobalt[147, 152-158], chromium[159], molybdenum[160], tungsten[160] and rhodium[161] *etc.* are also known. These two types of examples demonstrate that three and a half-membered ring structures are better described as π-allylic systems; with normal σ,π-bonds the system would suffer far too much strain (for further examples see [162-166]).

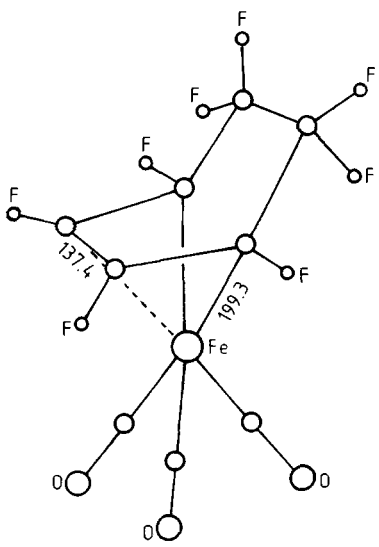
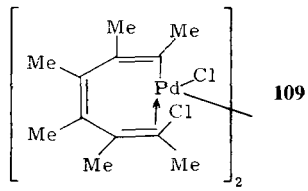


Fig. 4. Structure of tricarbonyl(octafluoro-1,3-cyclohexadiene)iron in the crystal. Bond lengths in pm [146].

5. Other Metallacyclic Compounds

So far, very little has been published about complexes containing ring systems with more than five and a half members. As example might be mentioned the product obtained on reaction of dichloro(benzonitrile)palladium with



109

2-butyne. The dinuclear complex **109** would appear to contain a six and a half membered ring system[167, 168] (for larger metallacycles see [169-171]).

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The Leukotrienes, Highly Biologically Active Substances Involved in Allergy and Inflammation

By Bengt Samuelsson*

Arachidonic acid, a fourfold unsaturated C_{20}-fatty acid, has attracted interest over the last 15 years far beyond the bounds of nutritional research. It forms an essential acyl component of the phospholipids in all animal cells. The long known fact that certain unsaturated fatty acids must be contained in the diet in order to ensure normal function of the organism has been explained by the discovery of a broad palette of biologically highly active oxidation products of arachidonic acid, a cascade, as it is often referred to. Arachidonic acid is formed in organisms from linoleic and linolenic acids, which belong to the so-called essential fatty acids. As early as 1935 *Ulf von Euler* was able to detect a substance in semen which caused smooth muscles to contract. This factor, which was later isolated in pure form, was termed prostaglandin. The number of prostaglandins, including the synthetically obtained analogues, then rapidly increased. Prostaglandins are biosynthesized from arachidonic acid and similar C_{20}-fatty acids by enzymatic oxidation with a cyclooxygenase. Its activity is inhibited by acetylsalicylic acid, indomethazine, and other substances, because these relieve or cure inflammations arising from the action of certain prostaglandins. After the prostaglandins, the thromboxanes, which promote aggregation of blood platelets and thus cause thrombosis, were discovered as further metabolic products of arachidonic acid. In a well-balanced equilibrium the thromboxanes have a biological effect completely opposite to that

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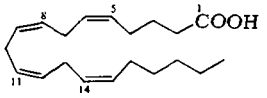
of prostacyclin, discovered soon after this, which inhibits platelet aggregation. Both of these biologically active substances are metabolites of arachidonic acid, and are formed in the course of the cyclizing oxidation. Aspirin and substances having a similar mode of action, therefore have an influence on thrombosis. There are, however, contraction processes and inflammation symptoms which do not respond to these substances, but to steroid hormones (cortisone). For symptoms of this type, to which asthma also belongs, the most recently discovered metabolic products of arachidonic acid are probably highly decisive; they are formed by another enzymatic route *via* a hydroperoxide of arachidonic acid. These compounds are formed in leukocytes and contain the triply unsaturated structural element of a triene and were, therefore, termed leukotrienes. Their astonishingly high histamine-like activity in producing contraction of lung capillaries, their marked property of making capillary vessels permeable to blood plasma, *i.e.* of generating oedema, the ability of leukotriene LTB_4 to cause adherence of human leukocytes and their adhesion to the endothelium, make the leukotrienes chemical mediators in allergies and inflammations, and produce biological effects when present at minute concentrations. In the following article one of the three scientists who were awarded this years Nobel prize for medicine and physiology, and who provided an explanation for this extraordinarily interesting class of natural products, gives an account of the conversion of arachidonic acid into the labile epoxide LTA_4 and further into the dihydroxy compound LTB_4 or the glutathione cysteinylglycine and cysteine conjugates LTC_4, LTD_4, and LTE_4, respectively, as well as of the physiological-pathological implications. The two other prize winners in this area of biologically active compounds, which are often referred to as eicosanoids, are *Samuelsson*'s teacher *Sune Bergström* and the Britain *John Vane*.

1. Introduction

Polyunsaturated fatty acids play a role as precursors of several biologically active derivatives. Thus, four main groups of derivatives, the prostaglandins, the thromboxanes, the prostacyclins, and the recently discovered leukotrienes, are formed by oxygenation and further transformation of various polyunsaturated fatty acids, particularly arachidonic acid **1**, a fourfold unsaturated C_{20}-fatty acid (5*Z*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid)[1,2]. These versatile, biologically active substances are also termed eicosanoids, after the number of C atoms they contain.



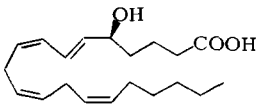
1

The leukotrienes exhibit three conjugated double bonds and usually form a thioether bond to cysteine: the latter type are of particular interest, since they are responsible for the biological activity referred to as "slow reacting substance of anaphylaxis" (SRS-A). These derivatives are potent bronchoconstrictors and seem to play a pathophysiological role in immediate hypersensitivity reactions. There is also evidence that both these compounds and a leukotriene with pronounced effects on leukocyte migration might function as mediators in inflammation. The present review summarizes the development of this new area of research.

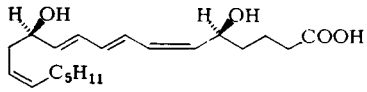
2. Metabolism of Arachidonic Acid in Leukocytes

It is now well established that aspirin and other nonsteroidal anti-inflammatory drugs inhibit the enzyme cyclooxygenase responsible for conversion of arachidonic acid into prostaglandins, thromboxanes, and prostacyclins[3]. Anti-inflammatory steroids prevent formation of prostaglandins by a different mechanism, *i.e.* by inhibition of the release of arachidonic acid from the phospholipid stores[4,5]. In view of the pronounced differences in the anti-inflammatory effects of steroids and aspirin-type drugs it seemed conceivable to us that arachidonic acid might generate additional pro-inflammatory derivatives whose formation is independent of cyclooxygenase. To test this possibility, we studied the metabolism of arachidonic acid in polymorphonuclear leukocytes (PMNL).

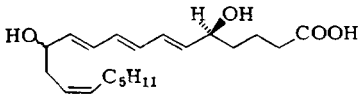
Using PMNL obtained from the peritoneal cavity of rabbits it was found that (5*S*)-5-hydroxy(6*E*,8*Z*,11*Z*,14*Z*)-eicosatetraenoic acid (5-HETE) **2** was the major arachidonic



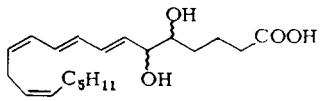
5-HETE **2**



5*S*, 12*R*-DHETE **3**



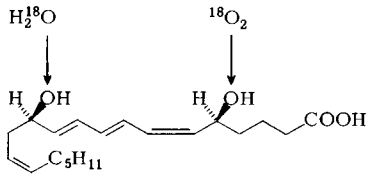
5*S*, 12*R*-DHETE **4a**
5*S*, 12*S*-DHETE **4b**



5,6-DHETE
Isomers **5a, b**

acid derived product[6]. Additional work showed that more polar products are also formed. These were identified as (5*S*,12*R*)-5,12-dihydroxy-(6*Z*,8*E*,10*E*,14*Z*)-eicosatetraenoic acid (major product), which was later termed leukotriene B_4, two additional (5*S*)-5,12-dihydroxy acids with (*E*,*E*,*E*,*Z*)-configuration (**4a**, **4b**), epimeric at C-12, and two isomeric 5,6-dihydroxy acids (**5a**, **5b**) with the same configuration of the 7,9,11,14-double bonds[7,8].

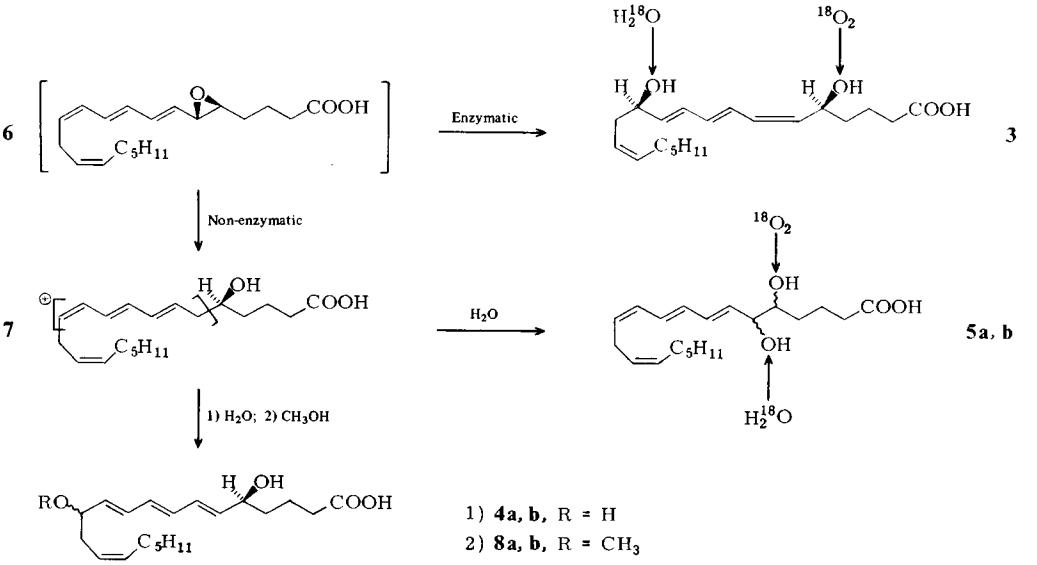
The occurrence of different double bond configurations in the products of the biological oxidation of arachidonic acid raised the question of the mechanism of their formation[8]. By means of ^{18}O labeling studies it could be demonstrated that the oxygen of the hydroxy group at C-5 originated from atmospheric O_2, whereas the oxygen of the hydroxy group at C-12 was derived from water[9]. On the basis of these observations, we postulated that the leukocytes generated an unstable intermediate which could undergo nucleophilic attack by water, alcohols, and other nucleophiles.



Rabbit PMNL were therefore incubated for 30 sec with arachidonic acid before addition of 10 times the volume of methanol or ethanol, or 0.2 volumes of 1 N hydrochloric acid. The products were analyzed by reversed-phase high performance liquid chromatography (RP-HPLC). The material formed upon trapping with methanol (or ethanol) contained two additional compounds (**8a** and **8b**) present in equal amounts in addition to compounds **2**–**5**. Their UV spectra indicated the presence of three conjugated double bonds, which were found to have an *E*-configuration as determined by IR spectroscopy. Gas chromatographic—mass spectrometric analyses of several derivatives of the two compounds showed that they were isomeric and carried hydroxy groups at C-5 and methoxy groups at C-12. Stereochemical analyses demonstrated that C-5 had an (*S*)-configuration. Although the configuration at C-12 was not determined it is clear that the compounds trapped with methanol are the C-12 epimers of (5*S*)-5-hydroxy-12-methoxy-(6*E*,8*E*,10*E*,14*Z*)-eicosatetraenoic acid. This indicated that a metabolite of arachidonic acid in leukocytes can undergo a facile nucleophilic reaction with alcohols. RP-HPLC analysis of samples obtained from trapping experiments performed under various conditions indicated that the amount of the 12-methoxy compounds **8a** and **8b** was always inversely proportional to the amount of 12-hydroxy acids **4a** and **4b**, thus suggesting that the latter are formed nonenzymatically from the same intermediate that gives rise to the alkoxy derivatives (cf. Scheme 1).

The stability of the intermediate was determined by incubating rabbit PMNL with arachidonic acid for 45 sec at pH 7.4 and 37 °C, suspending the resulting mixture in methanol and estimating the relative amounts of metabolites by RP-HPLC after various time intervals. The half-life of the intermediate was found to be 3—4 min. Simultaneously, the concentrations of compounds **4a**, **b**, **8a**, **b** and **5a**, **b** increased with time. The concentrations of **3** and **2** remained constant. This suggested that the other products are formed nonenzymatically by hydrolysis of a common unstable intermediate **6**, whereas **3** arises by enzymatic hydrolysis of the latter. Kinetic studies performed at various pH values indicated that the intermediate is acid-labile and is stabilized at alkaline pH.

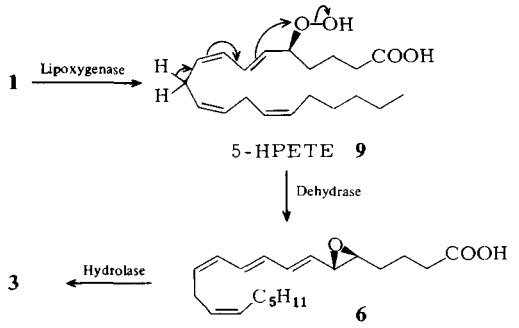
Based on these results, the structure (5*S*)-5,6-epoxy-7,9,11,14-eicosatetraenoic acid was proposed for intermediate **6**[9]. Hydrolysis of epoxides is acid catalyzed and opening of the rings of allylic epoxides is favored at allylic positions (C-6 in this case). This is consistent with the retention of ^{18}O at C-5 in the formation of the hydrolysis products **5a** and **5b** from the ^{18}O-labeled epoxide (formed by incubation of the leukocytes-arachidonic acid mixture with oxygen containing ^{18}O). The formation of all the hydrolysis products of the epoxide is shown in Scheme 1. Except for **3** these are formed by hydrolysis of the epoxide **6** *via* carbenium ion **7**. The latter adds hydroxyl anion preferentially at C-6 and C-12 to yield four isomeric products,



Scheme 1. Formation of dihydroxy derivatives from an unstable metabolite (epoxide **6**, LTA_4) of arachidonic acid.

which contain the stable conjugated triene structure. Compound **3** is formed enzymatically from the intermediate, since it has exclusively an (*R*)-configuration at C-12 and is only formed in nondenaturated cell preparations.

The pathway proposed for the biosynthesis of the epoxide **6** from arachidonic acid is shown in Scheme 2. It involves initial formation of 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE) **9**, from which the hydroxy compound **2** is formed by reduction. The epoxide **6** is formed from **9** by an intramolecular process, namely OH-elimination after abstraction of the proton at C-10, which is activated by two allyl groups.



Scheme 2. Formation of the unstable epoxide **6** (LTA_4) *via* the hydroperoxide **9** (5-HPETE).

The suggested structure of this 5,6-epoxide **6**, which is the same as that of leukotriene A_4 (LTA_4), has been confirmed by chemical synthesis whereby the stereochemistry was also elucidated[10]. The configuration of the three conjugated double bonds in leukotriene B_4 (LTB_4) was also determined using a synthetic approach[11]. LTA_4, the epoxide **6**, has recently been isolated from human polymorphonuclear leukocytes[12].

The recognition of the role of epoxide **6** in the transformation of arachidonic acid in leukocytes was a prerequisite for the work leading to elucidation of the structure and biogenesis of the "slow-reacting substance of anaphylaxis" (SRS-A)[9]. Thus, quantitative studies on the formation of the products of hydroxylation, **2** and **3**, from arachidonic acid by human PMNL demonstrated that the Ca-ionophore[*] A23187 stimulates the synthesis[13]. This was of particular interest since previous studies had shown that the ionophore also stimulates release of SRS-A from leukocytes[14]. Furthermore, the UV-absorption (λ_{max} about 270 nm) of the leukotrienes discovered in the leukocytes was similar to that reported for SRS-A[15,16]. The effects of the ionophore, the UV-absorbance data, and other considerations led us to develop the hypothesis that there was a biogenetic link between the unstable epoxide **6** and SRS-A[9].

3. Structure of the Slow-Reacting Substance of Anaphylaxis (SRS-A)

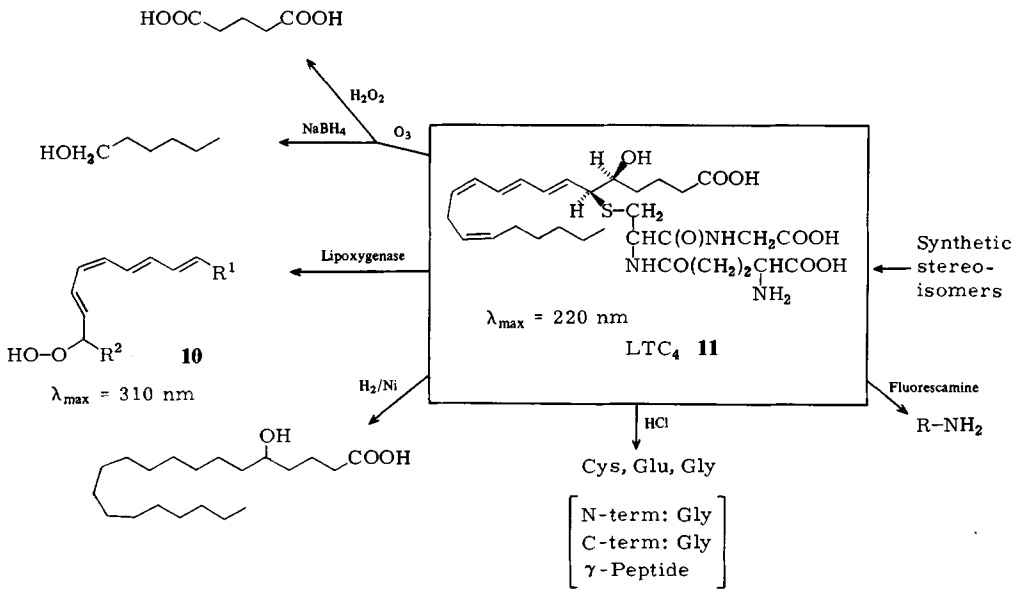
The term "slow-reacting substance" (SRS) was introduced in 1938 by *Feldberg* and *Kellaway* for a smooth muscle (guinea pig jejunum, part of the small intestine) contracting factor which appeared in the perfusate of guinea pig lung following treatment with cobra venom[17]. Subsequent studies have suggested that SRS is an important mediator in asthma and other types of immediate hypersensitivity reactions[18-21]. Immunologically released SRS is usually referred to as SRS-A (A for anaphylaxis), and is considered to be released together with other mediators (*e.g.* histamine and chemotactic factors) after interaction between immunoglobulin E (an antibody), bound to membrane receptors, *e.g.* to the bronchia, and antigens such as pollen *etc.* In the following, SRS and SRS-A are considered as practically identical. Previous structural work on SRS was severely limited by the difficulty in obtaining sufficient quantities of pure substance. However, it had been characterized as a polar lipid[16,22,23], possibly containing sulfur and having a UV spectrum with λ_{max} around 270 nm[15,16,24]. Studies with labeled arachidonic acid indicated that it was incorporated into SRS[25,26].

In preliminary studies employing different methods for production of SRS we found that murine mastocytoma cells treated with ionophore A23187 in presence of L-cysteine generated SRS in higher yields than previous procedures. This method also enabled formation of spasmogenic material antagonized by the SRS antagonist FPL 55712 and incorporation of isotopically labeled precursors[27]. The procedure used for isolation involved precipitation of protein with ethanol, alkaline hydrolysis, separation on Amberlite XAD-8 and silicic acid, and two steps of RP-HPLC. The material obtained by this procedure was essentially pure, showed a UV absorption maximum at 280 nm, and produced a characteristic contraction of guinea pig ileum which was reversed by FPL 55712[27]. The UV spectrum resembled those of the dihydroxy acids with three conjugated double bonds ($\lambda_{max} \approx 270$ nm) described in Section 2; however, the maximum was shifted 10 nm to higher wavelength. This is consistent with a sulfur substituent in the α-position to the conjugated triene. Experiments with labeled precursors showed that arachidonic acid and cysteine were incorporated into the products.

Degradation of SRS by desulfurization on Raney nickel afforded 5-hydroxyeicosanoic acid, which indicated that the arachidonic acid derivative and cysteine were linked by a thioether bond (cf. Scheme 3). The hydroxy group at C-5 in the fatty acid reinforced the hypothesis of a biogenetic relationship between the arachidonic acid metabolites and SRS, which we had found in leukocytes.

The positions of the double bonds in SRS biosynthesized from ^3H-labeled arachidonic acid were determined by reductive ozonolysis. This yielded [1-$^3H_1$] hexanol, demonstrating retention of the Δ^{14}-double bond of arachidonic acid. A unique method was used for locating the conjugated triene: Previous studies in our laboratory had shown that arachidonic acid and related fatty acids containing the homoconjugated system of two *cis*-double bonds at the terminal positions are peroxygenated by soybean lipoxygenase. Treatment of SRS with the lipoxygenase resulted in its conversion into the 15-hydroperoxide **10** of the conjugated tetraenoic acid, which was recognizable from a bathochromic shift of the UV maximum by 30 nm (Scheme 3). This indicated the presence of a Δ^{11}-(*Z*)-dou-

[*] Ionophores are molecules which channel ions, *e.g.* Ca^{2+}, through cell membranes.



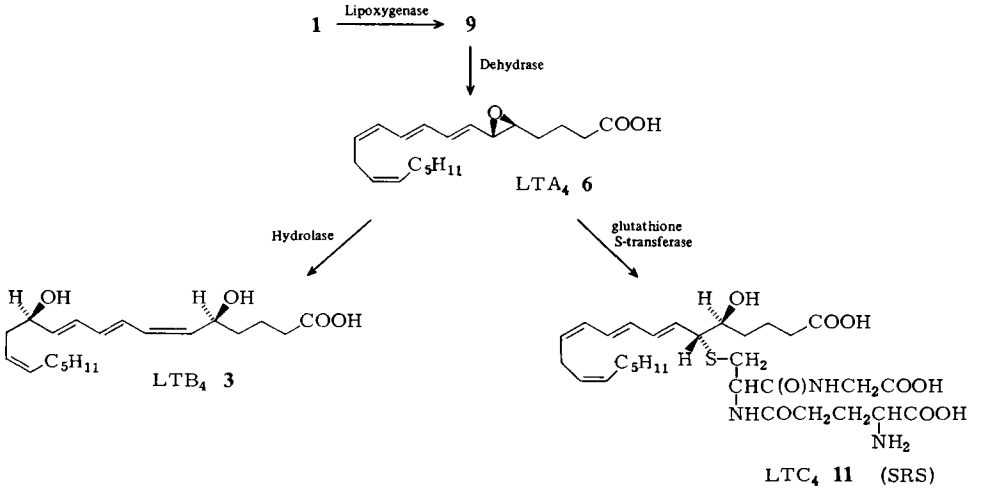
Scheme 3. Some reactions of SRS which account for its structure as leukotriene C_4 **11**.

ble bond and its conjugation with additional Δ^7- and Δ^9-double bonds. The structural studies at this stage showed that SRS was a derivative of 5-hydroxy-7,9,11,14-eicosatetraenoic acid with a cysteine-containing substituent linked in a thioether-manner at C-6.

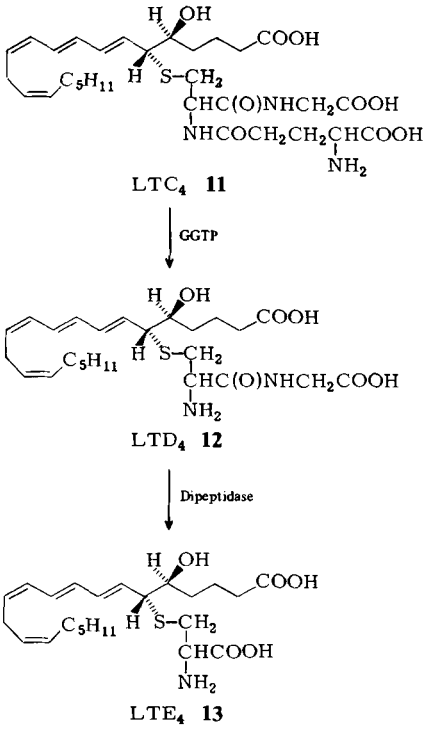
The fact that cysteine was bound was suggested by failure to isolate alanine after desulfurization. The cysteine-containing substituent was therefore referred to in the first publication as RSH[27-29]. Additional studies involving amino acid analyses of HCl-hydrolyzed SRS demonstrated that in addition to cysteine, glycine and glutamic acid were present in the ratio 1 : 1 : 1. The structure of the peptide, as determined by end group (dansyl method and hydrazinolysis) and sequence analyses (dansyl-Edman procedure), was γ-glutamylcysteinylglycine (glutathione). Accordingly, the structure of SRS obtained in murine mastocytoma cells from arachidonic acid and cysteine is 6-*S*-glutathionyl-5-hydroxy-7,9,11,14-eicosatetraenoic acid **11**, leukotriene C_4 (LTC_4)[30] (cf. Scheme 3).

The stereochemistry proposed for LTC_4 was confirmed and unambiguously assigned by its total synthesis, including preparation of stereoisomers, by *Corey et al.*[31]. The systematic name for LTC_4 is thus (5*S*,6*R*)-6*S*-glutathionyl-5-hydroxy-(7*Z*,9*Z*,11*E*,14*E*)-eicosatetraenoic acid. The previously proposed biogenetic relationship between the epoxide LTA_4 **6** and LTC_4 **11** has recently been confirmed by the conversion of synthetic LTA_4 into LTC_4 in human polymorphonuclear leukocytes[32]. The epoxide function of **6** is opened at the 6-position by the nucleophilic thio-function of glutathione to form a thioether (Scheme 4).

Note on Nomenclature: We chose the term "leukotriene" (LT), because the compounds were first detected in leukocytes and because their common structural feature is a conjugated triene[28]. Various members of the group have been designated alphabetically. Since the derivatives are formed not only from arachidonic acid (with 4 double bonds), but, in general, from C_{20}-fatty acids possessing the same 5,8,11-double bond system with more or less double bonds in the other half of the molecule, an additional numeration is needed[33]: referred to formula **6** LTA_n (n = 3, 4, or 5) are twofold to fivefold unsaturated 5,6-epoxy-7*Z*,9*Z*,11*E*-eicosanoic acids; LTB_n (5*S*,12*R*)-5,12-dihy-



Scheme 4. Formation of leukotrienes (LT) A_4, B_4, and C_4.



Scheme 5. Formation of leukotrienes (LT) D_4 and E_4.

droxy-(6*Z*,8*E*,10*E*)- (cf. **3**), LTC_n, (5*S*,6*R*)-6-*S*-glutathionyl-5-hydroxy-(7*E*,9*E*,11*Z*)-, LTD_n the corresponding *S*-cysteinylglycyl-, and LTE_n the simpler *S*-cysteinylpolyenoic C_{20} acids (cf. formulas **6**, **3**, **11**, **12**, and **13**, resp.).

The relationship of LTC_4, LTD_4 and LTE_4 is provided by the following observations. Studies with a different cell type, (rat basophilic leukemia cells, RBL-1), demonstrated that the major SRS species from this source was less polar than LTC_4 from leukocytes[34]. That the fatty acid part of this compound and LTC_4 were identical was indicated by their UV spectra, the products obtained after Raney nickel desulfurization, and the spectra changes observed after treatment with soybean lipoxygenase. Amino acid analyses, however, showed that the less polar product lacked glutamic acid. Edman-degradation indicated that glycine was C-terminal. Incubation of LTC_4 with γ-glutamyl transpeptidase (GGTP) provided additional proof for the structure. The product, the 6-*S*-cysteinylglycine compound LTD_4 (**12** in Scheme 5) was identical with the less polar product from RBL-1 cells. LTD_4 is more potent than LTC_4 in the guinea pig ileum bioassay and the contraction is faster[34].

The metabolism of LTC_3 has recently been studied using ^3H-labeled material of high specific activity, with the label in the fatty acid part of the molecule[35]. The results showed that guinea pig lung-homogenates rapidly converted LTC_3 to LTD_3. Liver and kidney homogenates did not catabolize LTC_3 appreciably. This was apparently due to high tissue concentrations of glutathione in the liver and kidneys. In accordance with these findings, labeled LTC_3 administered into the right atrium of male monkeys was rapidly transformed into LTD_3 and LTE_3[36]. The structures of leukotrienes have also been verified by chemical syntheses.

Leukotrienes have also been detected in the most varied of organs (Table 1). SRS-A is, therefore, a mixture of the sulfur-containing leukotrienes C_4, D_4, and E_4.

It has also been demonstrated recently that leukotrienes can be formed after initial oxygenation of arachidonic acid at C-15. Thus, the unstable 14,15-epoxy-5,8,10,12-eicosatetraenoic acid (14,15-LTA_4) is formed *via* the initially formed 15-hydroperoxide and is transformed into 14,15-dihydroxy-(14,15-LTB_4) and 8,15-dihydroxy-derivatives (8,15-LTB_4)[37,38]. A new isomer of LTB_4, (5*S*,12*S*)-5,12-dihydroxy-(6*E*,8*Z*,10*E*,14*Z*)-eicosatetraenoic acid, was recently isolated as a metabolite of arachidonic acid in human leukocytes[39]. This derivative is not formed *via* the leukotriene pathway and is therefore referred to as 5*S*,12*S*-DHETE.

4. Physiological Role of Leukotrienes

The "slow reacting substance of anaphylaxis" (SRS-A) has been characterized by some of its pharmacological effects. The classical contraction test on isolated guinea pig ileum relative to the analogous effect produced by histamine is a measure of the stimulating effect on smooth muscle, which is also responsible for the contraction of capillary blood vessels. An increase in the permeability of the blood vessels in guinea pig skin is recognized by the penetration of a dye into the tissue and formation of colored spots after the dye has been injected into the blood stream of the animal.

It has been suggested that SRS-A is an important mediator in asthma and other types of immediate hypersensitiv-

Table 1. Leukotrienes (LT) from arachidonic acid **1** in various organs.

Source	LTA_4	LTB_4	LTC_4	LTD_4	LTE_4	Ref.
Rabbit peritoneal leukocytes	+	+				[7, 9]
Human peripheral leukocytes	+	+	+			[12, 13, 58]
Mouse mastocytoma cells	+		+			[27, 30, 59]
Rat basophilic leukemia cells				+	+	[34, 60, 61]
Rat peritoneal monocytes			+	+		[62, 63]
Rat peritoneal cells (anaphylactic)			+	+	+	[64]
Rat leukocytes		+				[65, 66]
Rat macrophages		+				[67]
Mouse macrophages			+			[68]
Human lung			+	+		[69]
Guinea pig lung				+		[70]
Cat paws				+	+	[71]

ity reactions. The pure leukotrienes LTC_4 and LTD_4 (0.1—1.0 nM) caused concentration-dependent contractions of guinea pig ileum[40]. It was found that on a mol/L basis, histamine was 200 times less active than LTC_4. Both leukotrienes also increased vascular permeability in guinea pig skin[40,41].

Comparative studies have indicated essential differences in the mode of action of the sulfur containing leukotrienes and LTB_4. Recent studies with the pure leukotrienes have provided more detailed information about the effects on the pulmonary and cardiovascular systems: the cysteine-containing leukotrienes have specific effects on the micro-circulation. LTB_4 influences leukocyte migration by causing leukocyte adhesion to the endothelium in post-capillary venules and by potent chemotactic effects. These results indicate that the leukotrienes might be of importance as mediators in host defense mechanisms, such as immediate hypersensitivity and acute inflammatory reactions.

When administered intravenously, both LTC_4 and histamine increase the tracheal insufflation pressure in anesthetized and artificially ventilated guinea pigs[40,41]. In this respect LTC_4 is at least 100 times as potent as histamine and causes a longer lasting increase in insufflation pressure. When administered as an aerosol, LTC_4 is at least 1000-fold more potent than histamine. The effects of LTD_4 and LTE_4 are practically identical to those of LTC_4. We have also recently studied the bronchoconstrictor activity of LTC_4 in artificially ventilated monkeys[42]. LTC_4 (20 nmol, 1 g) caused a severe bronchoconstriction, as evidenced by a marked rise in transpulmonary pressure and a simultaneous fall in the partial pressure of arterial oxygen. This lasted 45—50 min. The findings indicated that cysteinyl-containing leukotrienes preferentially affect the peripheral airways, as previously suggested for crude SRS-A.

Human and monkey airway preparations also contract when administered LTC_4[43]. Human bronchi were found to be particularly sensitive. LTC_4 elicited contractions in the same low-dose range as in guinea pigs and it was at least 1000 times more potent than histamine. Airway preparations from monkeys were less reactive to both substances, but LTC_4 elicited significant contractions in approximately 100 times lower concentrations.

When injected intradermally into guinea pigs, LTC_4 and LTD_4 mimic the effects of crude SRS-A by causing extravasation of Evans' blue[40,41]. We have recently studied the microvascular actions of leukotrienes *in vivo* in more detail using the hamster cheek pouch preparation[44] (Fig. 1). When applied topically to the cheek pouch for a 3 min period, LTC_4 and LTD_4 (in concentrations ranging between 0.3 and 20 nM) elicited an intense dose-dependent contraction in particular terminal arterioles. The vasoconstriction was short-lived, and it was consistently followed by a dose-dependent, reversible leakage of macromolecules, as indicated by extravasation of fluorescein-conjugated dextran. The plasma leakage induced by these leukotrienes appeared at postcapillary venules. LTC_4, LTD_4 and LTE_4 all induced a significant increase of vascular permeability at much lower concentrations than histamine: LTC_4 is approximately 5000 times more potent than histamine in this respect. Administration of a vasodilator together with leukotrienes potentiates the increase in plasma leakage caused by a submaximal dose of leukotrienes, as has been reported in guinea pigs for the prostaglandin PGE_2 and LTD_4[45], and in guinea pigs, rabbits and rats for PGE_2 and LTE_4[46,47]. However, macromolecular leakage induced by LTC_4 is not affected by indomethacin or mepyramine, indicating that leukotrienes, *per se*, are highly effective.

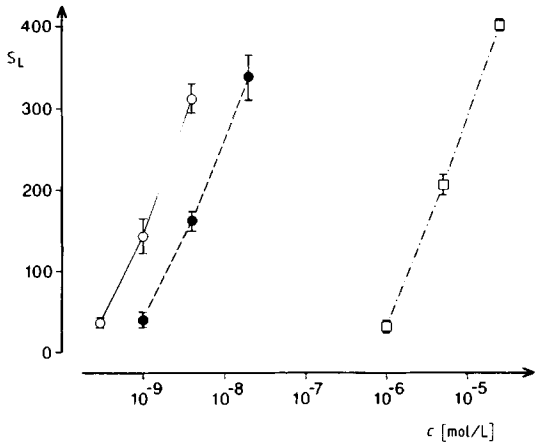


Fig. 1. Increase in vascular permeability of the hamster cheek pouch caused by leukotrienes (LTC_4 O—O, LTD_4 ●---●) and by histamine (□-·-□). S_L = number of plasma leakage outlets per cm^2.

Administration of LTB_4 to the hamster cheek pouch in the same dose-range as LTC_4 did not elicite vasoconstriction, and had no effects on plasma leakage. However, LTB_4 causes a dramatic increase in leukocyte adhesion to endothelium in small venules[44]. Upon addition of LTB_4, marginating leukocytes immediately started to roll slower and there was a pronounced increase in the number of leukocytes adhering to the endothelium. Increased adherence of human leukocytes caused by LTB_4 has also been demonstrated *in vitro* using a column of nylon fibers[48] (cf. Fig. 2).

The number of interstitial white cells increased during the superfusion with LTB_4 (6–10 min). This finding is consistent with the chemotactic stimulant property of LTB_4. The chemotactic effect of LTB_4 has been demonstrated, *in vitro*, using either the so-called Boyden chamber technique or migration under agarose[49–52]. This effect has been monitored, *in vivo*, by determining white cell accumulation in the peritoneal cavity of guinea pigs following intraperitoneal injection of LTB_4[53]. According to the results, LTB_4 might be a mediator in the migration of leukocytes from the blood to areas of inflammation. It is of interest in this context that the chemotactic peptide, formylmethionylleucylphenylalanine (fMLP) stimulates the formation of LTB_4 and other leukotrienes in human neutrophils[54].

Our results indicate that both leukotrienes and cyclooxygenase products of arachidonic acid, such as prostaglandins, are of importance in immediate hypersensitivity reactions and inflammation. The cysteine-containing leukotrienes, formed by another oxidation route, are potent stimulants of pulmonary smooth muscle with specific effects, *in vivo*, on peripheral airways. They also induce plasma leakage from postcapillary venules. These biologi-

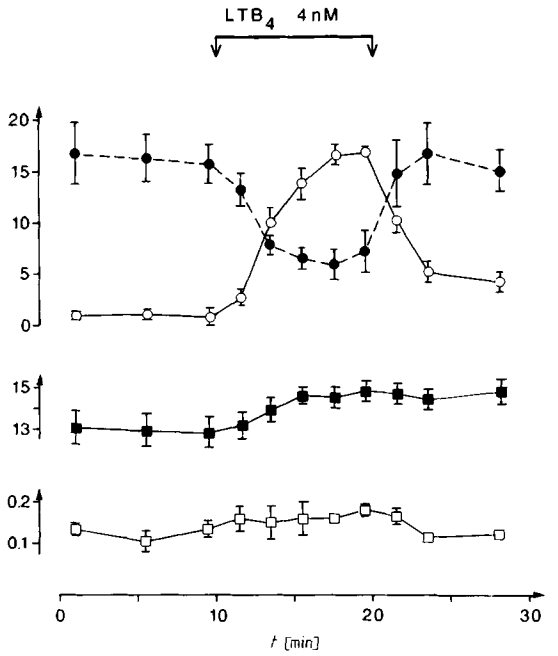


Fig. 2. Measurement of the activity of LTB_4 (4 nM) at a postcapillary venule of the hamster cheek pouch. Top: Leukocytes; number of cells marginating per minute (●) and number adhering to the endothelium (○). Middle: temporal change of the venule diameter (μm). Bottom: erythrocytes: velocity (mm/s).

cal effects indicate that they might function as mediators in airway and skin manifestations of immunological origin. However, the biological effects of these sulfur-containing leukotrienes and of LTB_4 indicate that they might be involved in inflammatory reactions of a more general character. The ability of LTB_4 to cause leukocyte adhesion to the endothelium in postcapillary venules and to stimulate leukocyte chemotaxis indicate that the leukotrienes participate in host defence reactions against various noxious stimuli. The combined effects of LTB_4 and LTC_4 and metabolites are reminiscent of the early phase of acute inflammation.

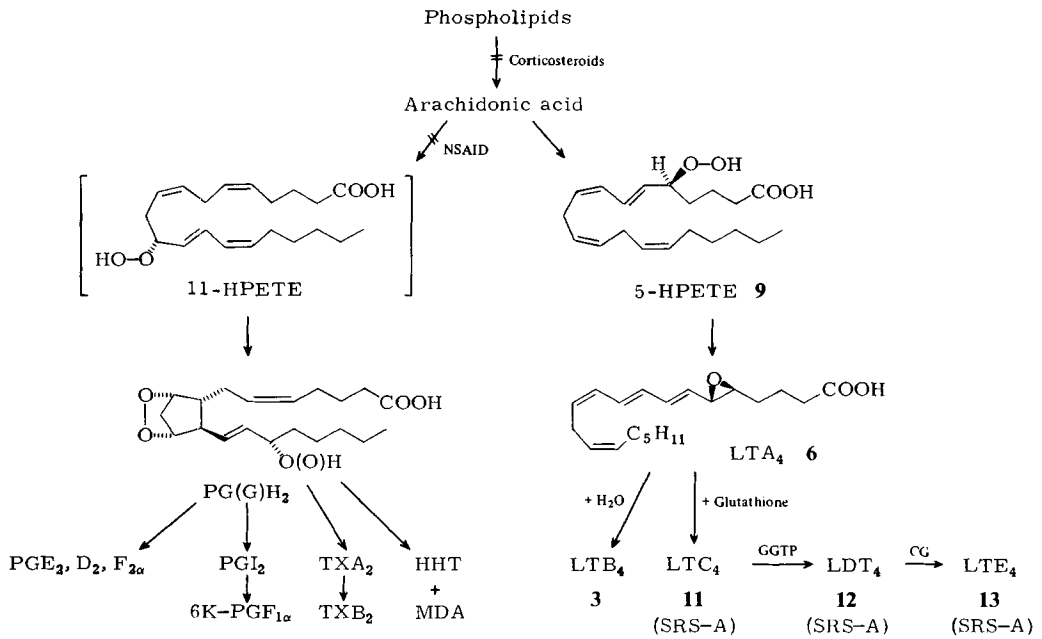
The leukotrienes and some metabolites resulting from the cyclooxygenase route from arachidonic acids have effects which are complimentary: prostaglandins, thromboxanes, prostacyclins. Hence the synergism between the leukotrienes, causing plasma leakage, and the vasodilators prostaglandin PGE_2 and prostacyclin PGI_2 might be of importance in the formation of oedema. Furthermore, synergistic effects between the leukotrienes, with bronchoconstrictor properties, and thromboxane A_2 are also conceivable. LTC_4 and LTD_4 cause release of TXA_2 in guinea pig lung[55]: TXA_2 is a potent constrictor of airways, and its release might contribute to the bronchospasm in allergic manifestations.

The interrelationship between the cyclooxygenase pathway (yielding prostaglandins and thromboxanes) and the leukotriene pathway is illustrated in Scheme 6.

Anti-inflammatory steroids prevent the release of the precursor arachidonic acid from the phospholipids of cell membranes, whereas cyclooxygenase inhibitors, such as aspirin, block the transformation of this acid into prostaglandins, thromboxanes, and prostacyclins. It has recently been proposed that anti-inflammatory steroids act by stimulating the synthesis of an inhibitor of phospholipase A_2[56,57]. By inhibiting the release of arachidonic acid, steroids prevent formation, not only of prostaglandins and thromboxanes, but also of leukotrienes and other oxygenated derivatives. The inhibition of leukotriene formation might be responsible for some of the therapeutic effects of steroids which are not shared by aspirin type drugs.

5. Outlook

The new knowledge about leukotrienes and their biochemical relatives[72] summarized in this article suggests



Scheme 6. Formation of prostaglandins (PG), thromboxanes (TX), prostacyclins (PGI_2), and leukotrienes (LT). NSAID: non-steroidal anti-inflammatory drugs; HHT: (12*S*)-12-hydroxy-(5*Z*,8*E*,10*E*)-heptadecatrienoic acid.

new possibilities for the development of novel and more specific therapeutic agents, particularly in diseases related to immediate hypersensitivity reactions and inflammation. Such drugs might be based on antagonism of end-products or inhibition of enzymes involved in the generation and further transformation of the key intermediate, LTA_4. Furthermore, compounds which have inhibitory effects involving both the cyclooxygenase pathway and the leukotriene pathway from arachidonic acid might be of significant importance.

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$CrTe_3$—A Novel Transition-Metal Polytelluride

By *Kurt O. Klepp** and *Herbert Ipser*

We have been able to detect a previously unknown intermediate phase in the tellurium-rich field of the binary system chromium-tellurium[3]. This phase is formed in a peritectic reaction at 753 ± 3 K. Its composition, established as $CrTe_3$ from powder diffraction and thermoanalytical studies, indicated a polytelluride of chromium. Since higher polytellurides of 3d-elements were previously unknown, the structural characterization of this compound appeared to be particularly desirable. Single crystals for the structural investigation were obtained by annealing a stoichiometric mixture of the elements at 690 K for four months in the presence of Al_2Cl_6 and HCl as mineralizing agents.

As expected from its lamellar crystal habit, $CrTe_3$ crystallizes in a layered structure. Composite layers are formed (Fig. 1) which run parallel to the *bc*-plane. They consist of building groups of four edge-linked $CrTe_6$-octahedra which are connected according to $Cr_4Te_8Te_{8/2}$ *via* shared apical tellurium atoms to give a two-dimensional infinite arrangement. In addition these building groups are linked together *via* Te—Te bonds giving rise to the formation of Te_2 and Te_3 moieties. Only weak interactions, however, occur between the composite layers. $CrTe_3$ is a complex polyanionic compound which could be formulated ionically as $[Cr^{3+}]_2[Te^{2-}][Te_2^{2-}][Te_3^{2-}]$. The Te—Te distances of 282 pm are only slightly larger than the length of a Te—Te single bond (274 pm). The occurrence of Te_3-chains is surprising, since transition-metal compounds containing this polyanion were previously not known.

In common with the other chromium chalcogenides, whose structures can be derived from the NiAs-type, $CrTe_3$ shows octahedral coordination of the transition metal atom as well as the formation of close-packed chalcogen layers. These layers are slightly puckered and run—in contrast to the composite layers formed by chemical bonds—parallel to the *ac*-plane. Their stacking, however, no longer corresponds to a three-dimensional close-packing. This is due to the formation of the Te—Te bonds, which occurs between these layers and which causes them to be puckered. The Cr—Te distances (270—276 pm) are comparable with those in other chromium tellurides.

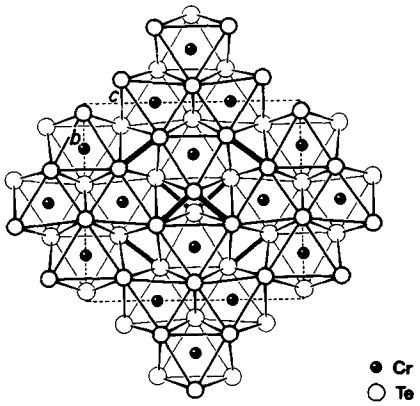

Fig. 1. Projection of the $^2_\infty[CrTe_3]$ composite layer on the *bc*-plane. Tellurium-tellurium bonds are indicated by thick lines. Crystallographic data: space group $P2_1/c$, $a = 788.7(6)$, $b = 1122(2)$, $c = 1156(1)$ pm, $\beta = 118.41(2)°$, $Z = 8$; $R = 0.054$, $R_w = 0.063$ (1063 reflections with $I > 3\sigma(I)$, 74 refined parameters). The Te—Te bond lengths are 281.6(3) pm for the Te_2 dumbbell, 281.7(3) and 282.4(3) pm for the Te_3 chains. The bond angle in the chain is 86.17(7)°. The Cr—Te distances lie between 270.0 (s) and 275.6(5) pm. Further details on the crystal structure determination can be obtained from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, by quoting the depository number CSD 50298, the name of the author and complete citation of the journal.

The building principle realized in the layered structure of $CrTe_3$ differs essentially from those of the previously known transition-metal trichalcogenides[12], which are predominantly formed by the elements of groups IVb and Vb. Here the transition metal atom is in a trigonal-prismatic environment; the polyanions are formed by chalcogen dumbbells which are coordinated "side on" to the transition-metal atom. In $CrTe_3$, however, as in pyrites, two homonuclearly bonded chalcogen atoms are coordinated to different transition metal atoms.

$CrTe_3$, apart from TiS_3[13] and VS_4[14], is the third higher polychalcogenide of a 3d-element whose crystal structure has been established. The formation of a metastable chromium polysulfide of composition Cr_2S_5 has been described[15]. A polytelluride of this stoichiometry is likely to exist as an equilibrium phase in the chromium-tellurium system[3]. Initial studies lead one to expect a close structural relationship to $CrTe_3$.

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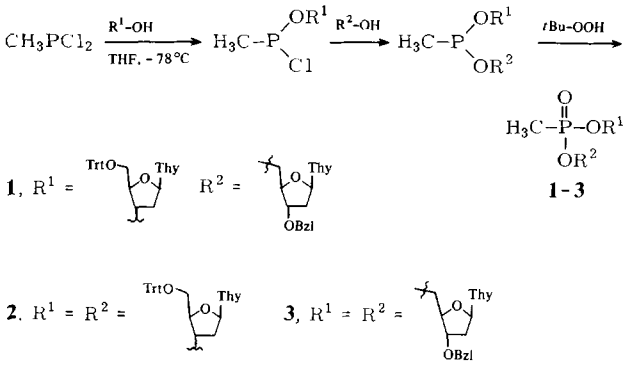
A Novel Synthesis of Nucleoside Methylphosphonates

By *Joachim Engels** and *Alfred Jäger*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

Nonionic analogues of DNA are of interest in the study of DNA-DNA and DNA-protein interactions. In this connection, phosphonic acid esters of deoxyribonucleosides should be particularly suitable because of their chemical stability.

We report here a novel two-step route to nucleoside methylphosphonic acid esters, involving the direct synthesis of phosphonous acid esters and their subsequent oxidation[1]. Dichloro(methyl)phosphane is treated successively with two protected nucleosides in a one-pot reaction at −78 °C in tetrahydrofuran (THF). The resulting dinucleoside methylphosphonic acid diester is not isolated but oxidized to the corresponding methylphosphonate by addition of *tert*-butyl hydroperoxide (Scheme 1).



Scheme 1. Trt = trityl; Thy = thymine residue.

When CH_3PCl_2 is treated with two equivalents of 5′-*O*-tritylthymidine *or* 3′-*O*-benzoylthymidine, the symmetric 3′,3′- or 5′,5′-linked phosphonates **2** or **3** are accessible.

Reaction of 5′-*O*-tritylthymidine (R^1—OH) and 3′-*O*-benzoylthymidine (R^2—OH) with CH_3PCl_2 affords **1** (81%) with 3′,5′-methylphosphonate-internucleotide bonding. The 3′,3′-phosphonate **2** always occurs as a side product (8%), whereas formation of **3** (by reaction of 3′-*O*-benzoylthymidine with unconsumed CH_3PCl_2) can be avoided by using a slight excess (0.06 equiv.) of 5′-*O*-tritylthymidine.

1 consists of two diastereomers, which can be separated by thin layer chromatography: the P—CH_3 group exhibits two doublets in the ^{1}H-NMR spectrum. Although CH_3PCl_2 is not a sterically demanding reagent, the reaction nevertheless proceeds more stereoselectively than the synthesis of dinucleoside methylphosphonate derivatives by *Ts'o et al.*, which results in a 1 : 1.5 isomer ratio[2]; using the method described here we obtained the diastereomers of **1** in the ratio 4 : 1, whereby the major product is the isomer with the larger R_f value. Selectivity only occurs, however, when 5′-*O*-tritylthymidine is the first alcohol component. Each of the two isomers was converted into the corresponding dinucleoside methylphosphonate T*p*T[3] by debenzoylation with *tert*-butylamine and detritylation with $BF_3 \cdot OEt_2$. The NMR spectrum of the major deblocked product is identical with that of $(TpT)_1$, described by *Ts'o et al.*, and that of the other isomer with $(TpT)_2$[4].

The phosphonic acid ester intermediate also reacts smoothly with sulfur and selenium and, hence, opens up a route to the previously unknown thio- and selenophosphonate analogues. Because of the similarity with the phosphite method of *Letsinger et al.*[5], this synthetic route can also be combined with the Letsinger-DNA synthesis.

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Novel Metastable Germanium Modifications *allo*-Ge and 4H-Ge from Li_7Ge_{12}

By *Andreas Grüttner, Reinhard Nesper*, and *Hans Georg von Schnering**

Dedicated to Professor Albrecht Rabenau on the occasion of his 60th birthday

A renewed investigation of the binary systems Li-Si[1] and Li-Ge[2,3] led to discovery of the phase Li_7Ge_{12}; it is formed as leaf-shaped metallic gray crystals on cooling a stoichiometric melt of the elements (Ta-crucible; ∅ up to 3 cm; $T_{max} = 1025$ K). The compound crystallizes orthorhombically with a structure (Fig. 1) containing a characteristic complex two-dimensional infinite polyanion $^2_\infty[Ge_{12}^{7-}]$[5]. One of the Li atoms is situated in a Ge cage, the other six are intercalated between the Ge layers [$Pmn2_1$ (No. 31); $a = 11.541(3)$, $b = 8.073(2)$, $c = 15.359(4)$ Å; $Z = 4$; 1788 *hkl*, $R = 0.07$]. The outstanding chemical property of Li_7Ge_{12} is the spontaneous evolution of H_2 on reaction with protic solvents, leading to topotactic formation of *allo*-germanium[5], a novel metastable Ge-modification[4]. The H_2 is extruded strictly parallel to the layers of the two-dimensional anion; at the same time, a linking of adjacent layers takes place with formation of a three-dimensional structure (Fig. 1). *allo*-Ge is formed in these reactions as gray shiny metallic frits or leaflets which can be ground like graphite. Single crystals of *allo*-Ge are formed on reaction of Li_7Ge_{12} single crystals with benzophenone in tetrahydrofuran, whereby strong topotactic demetalation of Li_7Ge_{12} leads to Li^+ and the radical anion of Ph_2CO. Mechanical strains in *allo*-Ge crystals are largely avoided under these mild conditions.

allo-Germanium is a diamagnetic semiconductor. It crystallizes orthorhombically with considerable stacking disorder [$Pmc2_1$ (No. 26): $a = n * 23.887(9)$, $b = 7.787(3)$,

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$c = 16.304(5)$ Å; $Z = 128$]. The essential structural unit is the original two-dimensional polyanion of Li_7Ge_{12}, resulting from homonuclearly coupled four-, three- and two-bonded atoms of the type $(4b)Ge^0$, $(3b)Ge^{1-}$ and $(2b)Ge^{2-}$. The valences that become free on demetalation are saturated by new Ge—Ge bonds within the layers and between adjacent layers, so that only atoms of type $(4b)Ge^0$ are still present (Fig. 1).

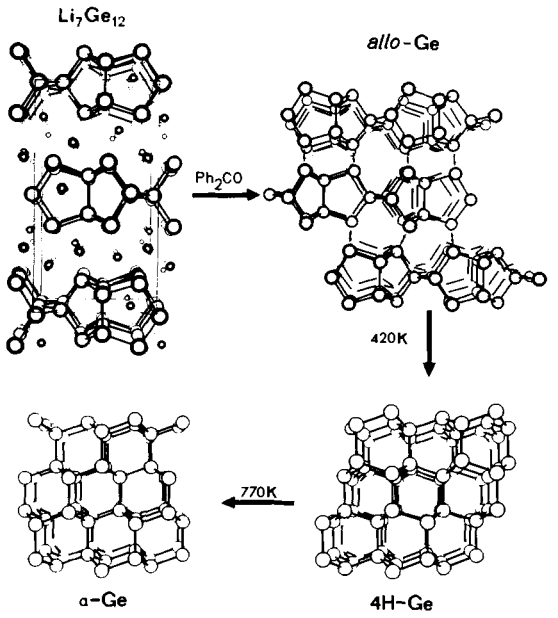

Fig. 1. Formation of the novel Ge modifications *allo*-Ge and 4H-Ge. *allo*-Ge (schematic) is formed in a strongly topotactic reaction from Li_7Ge_{12}; it is not converted directly into α-Ge, but firstly into 4H-Ge, which, so far, has only been obtained in this way. The slow transformation from the 4H-Ge into the α-Ge phase commences at 770 K.

On heating under inert conditions, *allo*-Ge is exothermally and irreversibly converted at 420 K into a further metastable Ge-modification. In this form, germanium crystallizes hexagonally with the known structure of the polymorphic compound 4H-SiC. The novel modification 4H-Ge[5] could previously be obtained only in the powdered form [$P6_3mc$ (No. 186); $a = 3.989$ Å, $c = 13.107$ Å; $Z = 8$; $c/a = 3.286$]. On further prolonged heating, the similarly exothermic conversion of 4H-Ge into the stable α-Ge commences at 770 K.

On rapid heating 4H-Ge melts at 1198 K, *i.e.* 10 K below αGe. The formation of *allo*-Ge from Li_7Ge_{12} encourages increased activity in the search for metastable forms of the elements.

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Cyclobutadienes or Acetylenes from (2-Cyclopropen-1-yl)carbenes— A Question of Spin Multiplicity?**

By *Philipp Eisenbarth* and *Manfred Regitz**

Diazomethylcyclopropenes such as **1a**[1] or **1b**[2] are promising precursors for the synthesis of cyclobutadienes. Thus, on irradiation in pentane, they afford the tri-*tert*-butylcyclobutadienecarboxylates **5a**[1] (Table 1) and **5b**[2], respectively, together with the 3-hexyne **3** and the pentynoates **4a** and **4b**. The formation of alkynes in the photolysis of **1b**[2] was overlooked. In both cases, the ratio of cyclobutadiene formation to acetylene fragmentation is *ca.* 70:30 and is markedly dependent upon temperature and solvent.

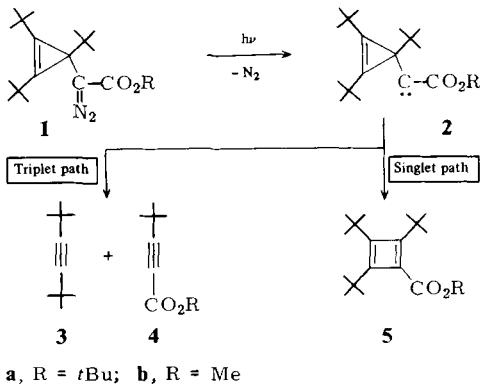
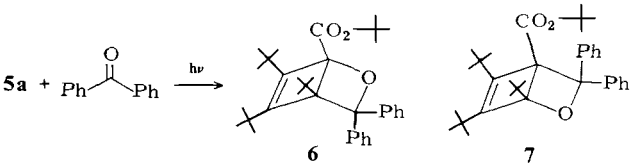


Table 1. (Selected data). Yields and physical and spectroscopic properties of **5a** and **6**.

5a: 67%; orange crystals; m.p. = 56—57 °C; b.p. = 155—156 °C/0.1 torr; ^{1}H-NMR ($CDCl_3$): $\delta = 1.14$ (s, 18H), 1.16 (s, 9H), 1.46 (s, 9H)
6: 20%; colorless crystals; m.p. = 175—177 °C; ^{1}H-NMR ($CDCl_3$): $\delta = 0.87$, 1.15, 1.31, 1.44 (in each case s, in each case 9H), 7.10—8.20 (m, 10H)

What is the reason for this diversion in reaction behavior? By analogy to the Wolff rearrangement[3], singlet-**2** should rearrange (**2** → **5**) and triplet-**2** ought to fragment (**2** → **3** + **4**)[4]. Sensitization of the reaction with benzophenone should decisively influence the product ratio. The experiment with **1a** confirms this supposition (**5a** : **3** + **4a** = 20 : 70, 10% unidentified products). In any case, the excess of sensitizer reacts with **5a** in a [2 + 2]-cycloaddition to give the 2-oxabicyclo[2.2.0]hex-5-ene derivative **6** (7%)[5] (*Table 1*). *To our knowledge photochemical cycloadditions of cyclobutadienes have so far never been reported in the literature.*



The question as to whether **3** and **4a** could also be formed from **5a** by benzophenone-sensitized photolysis

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can be answered in the negative. Under these conditions only the previously mentioned cycloaddition of the sensitizer is observed (20%); it does not take place if one forgoes the irradiation.

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[2] S. Masamune, N. Nakamura, M. Suda, H. Ona, *J. Am. Chem. Soc. 95* (1973) 8481.
[3] Only singlet-carbenes react in a Wolff rearrangement: W. J. Baron, M. R. DeCamp, M. E. Hendrick, M. Jones, R. H. Levin, M. B. Sohn in M. Jones, R. A. Moss: *Carbenes 1*, Wiley, New York 1973, p. 120.
[4] There are only few confirmed examples of this reaction; *e.g.* a) M. Regitz, A. Heydt, B. Weber, *Angew. Chem. 91* (1979) 566; *Angew. Chem. Int. Ed. Engl. 18* (1979) 531; b) G. Maier, M. Hoppe, H. P. Reisenauer, C. Krüger, *ibid. 94* (1982) 445; *21* (1982) 437; *Angew. Chem. Suppl. 1982*, 1061.
[5] That the cycloaddition takes place at the electron-deficient double bond is revealed by the spectroscopic data of **6**. Evidence against the reversed orientation of the reaction partners in the cycloaddition (formation of **7**) is provided by the fact that a *tert*-butyl group is shifted markedly upfield ($\delta = 0.87$, anisotropic effect of a phenyl ring).

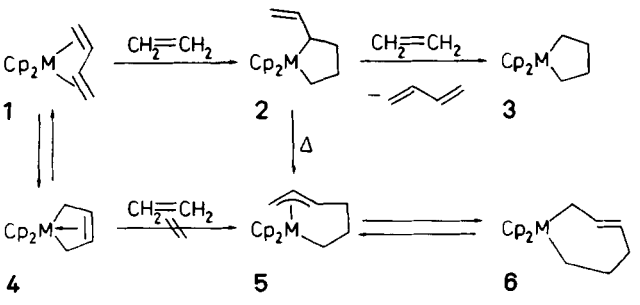
The Reaction of (Butadiene)zirconocene and -hafnocene with Ethylene**

By *Gerhard Erker**, *Klaus Engel*, *Ulrich Dorf*, *Jerry L. Atwood*, and *William E. Hunter*

In the coupling of olefinic substrates on early transition metals, reaction mechanisms *via* metallacycles can be favored over the conventional olefin-insertion mechanisms[1b]. Such likely competition should lead to (*s-trans*-butadiene)metallocene **1** and (*s-cis*-butadiene)metallocene **4**—isomers with markedly different σ-complex character[2]—exhibiting different reaction behavior towards ethylene.

We have now found that in the equilibrium mixture **1a** ⇌ **4a**, exclusively (*s-trans*-η^4-butadiene)zirconocene **1a** reacts with ethylene under mild conditions; the zirconacyclopentane **3a**[5] and (1-3:6-η-hexenylene)zirconocene **5a** (Fig. 1) are formed in a ratio which is temperature-dependent.

(*s-cis*-Butadiene)hafnocene **4b** does not react with ethylene at temperatures up to 120 °C. On the other hand, **1b** already reacts at −10 °C with ethylene in a 1:1 ratio to give the cyclic σ-allyl complex **2b**[6]. At room temperature, further reaction with ethylene leads to formation of **3b**[5b] and liberation of butadiene. At 25 °C, **2b** rapidly rearranges to the isomeric π-allyl complex **5b** in the absence of ethylene.



a, M = Zr; **b**, M = Hf; Cp = η^5-C_5H_5

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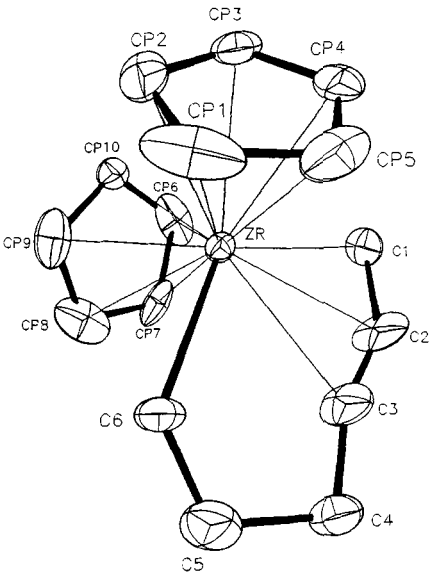

Fig. 1. Structure of **5a** in the crystal. Most important bond lengths: Zr—C1 246(1), Zr—C2 248(1), Zr—C3 264(1), Zr—C6 241(1), Zr—C_{Cp} (mean value) 251(3) pm.

The dynamic NMR spectra of the π-allyl complexes indicate equilibration with the σ-allyl compounds **6**. From the coalescence of the Cp resonances in the ^{1}H-NMR spectrum, a Gibbs activation barrier of $\Delta G^{\ddagger}_{50\,°C}(\mathbf{5b}) = 17.6$ kcal mol^{-1} [$\Delta G^{\ddagger}_{114\,°C}(\mathbf{5a}) = 21.0$ kcal mol^{-1}] has been determined for the automerization of **5** *via* **6**.

The finding that **5** is not accessible from **4** by direct insertion of ethylene but only from **1** *via* intermediate **2** demonstrates that a mechanism involving a metallacycle can also supersede the "classical" insertion mechanism in the coupling of ethylene with butadiene[8].

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[6] For the regioselectivity of five-membered ring formation, see: A. Stockis, R. Hoffmann, *J. Am. Chem. Soc. 102* (1980) 2952.
[8] A. C. L. Su, *Adv. Organomet. Chem. 17* (1979) 269.

Catalyst Deactivation during Zirconocene- and Hafnocene-Induced Ethylene Dimerization**

By *Ulrich Dorf*, *Klaus Engel*, and *Gerhard Erker**

The factors leading to the termination of catalytic reaction cycles are generally very difficult to assess due to the

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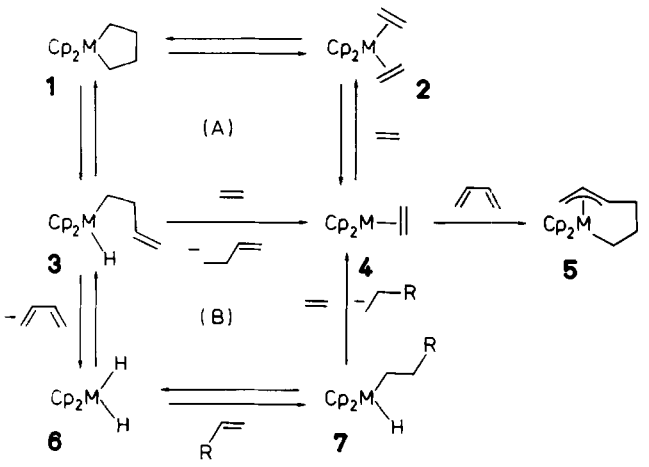
comparatively small amounts of active catalyst relative to other participating components. Zirconocene- and hafnocene-induced ethylene dimerization now provides a system in which the course of stoichiometric consumption of the catalyst can be monitored, because of comparable rates of propagation and termination of the chain.

When a solution of the zirconacyclopentane **1b** in ethylene-saturated toluene is heated to 60 °C, consumption of the olefin takes place slowly (≈1 equiv./Zr in 3 h). As organic products, 1-butene and ethane are formed at first, then on prolonged reaction, increasing amounts of *n*-butane. After 24 h at 60 °C there results a mixture of *n*-butane (0.94 equiv./Zr), 1-butene (0.66), and ethane (0.06). After this period of time the metal-induced transformation of ethylene has come to an end. The metallacycle **1b** has been quantitatively converted into the catalytically inactive (1—3:6-η-hexenylene)zirconocene **5b**[3]. A similar mixture is obtained on reaction of the oligomeric hydride $(Cp_2ZrH_2)_x$ with ethylene.

5b, which can be regarded as the product of the linkage of ethylene with butadiene on the zirconocene moiety, is formed in good yields under mild conditions, not only on reaction of (*s-trans*-η⁴-butadiene)zirconocene and ethylene[3], but also on reaction of the zirconacyclopentane **1b** or $(Cp_2ZrH_2)_x$ with butadiene.



a, M = Ti; **b**, M = Zr; **c**, M = Hf; Cp = η⁵-C_5H_5

The dimerization of ethylene induced by metallacyclopentane **1** can readily be explained in terms of a reaction sequence involving β-hydride elimination to give **3**, followed by reductive elimination to give **4**. Further reaction of **4** with ethylene leads to regeneration of the starting material **1** *via* the intermediate **2** (catalysis cycle (A)).

n-Alkanes are presumably formed by a competing reaction sequence starting with a further β-hydride elimination from **3**, affording butadiene, and leading to **6**[7]. After hydrogenation of alkene present in the solution by the hydride complex **6**, **4** is generated *via* **7**. According to our observations it may be assumed that the (olefin)metallocene complex **4** is very efficiently trapped by the butadiene formed in reaction cycle (B) with formation of the catalytically inactive **5**.

A corresponding reaction mechanism is observed in the case of the markedly less reactive hafnocene system. **1c** reacts with butadiene at 90 °C to give **5c**[3] and ethylene. At 110 °C, a slow dimerization of ethylene induced by **1c** can be observed. Thereby, a notable amount of **5c** is formed. Accordingly, in this system also, the active catalyst is consumed by a trapping reaction with a direct product of the reaction cycle[11].

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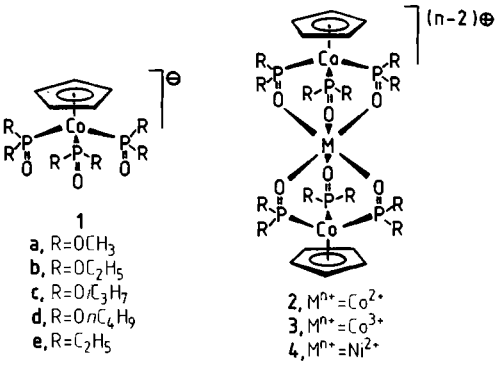
[7] J. D. Fellmann, R. R. Schrock, G. A. Rupprecht, *J. Am. Chem. Soc. 103* (1981) 5752; J. M. Mayer, J. E. Bercaw, *ibid. 104* (1982) 2157.
[11] In contrast to **1b** and **1c** the titanacyclopentane **1a** does not react with butadiene to give **5a**. With ethylene, a slow thermally induced reaction is in fact observed, but in competition a rapid unspecific decomposition of **1a** takes place (*ca.* 95% decomposition in ethylene-saturated toluene solution after 30 min at 70 °C). The resulting C_4 fraction (≈1.5 equiv./Ti) consists of *n*-butane (7.0%), 1-butene (15.4%), *cis*- and *trans*-2-butene (46.0%), and butadiene (31.6%); cf. G. P. Pez, *J. Chem. Soc. Chem. Commun. 1977*, 560.

Steric and Electronic Control of Ligand Field Strength in Octahedral Co^{3+} Spin-Crossover Complexes**

By *Werner Eberspach, Nabil El Murr,* and *Wolfgang Kläui**

In octahedral transition-metal complexes with d^4, d^5, d^6, or d^7 electron configuration a thermal equilibrium between the low-spin and high-spin form can be observed if the condition ligand field splitting ≙ spin pairing energy is fulfilled. All previously known Co^{3+}-d^6 complexes—with exception of the magnetically normal CoF_6^{3-} ion—are present in the diamagnetic "low spin" form. Recently, we were able to synthesize the organometallic oxygen ligand **1b**, which is weak enough and sufficiently hard[1] to induce a spin equilibrium in a Co^{3+} complex[2]. We have now found that the spin equilibrium can be so controlled by variation of the substituents R that at room temperature completely diamagnetic through to essentially paramagnetic Co^{3+} complexes of type **3** can be obtained. The synthesis of the Co^{3+} complexes **3a—e** was achieved by oxi-



dation of the Co^{2+} compounds **2a—e**—either electrochemically[3] or by means of tri(*p*-bromophenyl)ammoniumyl radical cations. Compounds of the cations **3a—d** (*e.g.* ClO_4- or PF_6-salts), which are dark green at room tempera-

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ture, turn bright yellow on cooling, and *vice versa, i.e.* they are thermochromic. **3e** is yellow and shows no thermochromism. The change in color of the Co^{3+}-complexes with decreasing temperature is accompanied by a decrease in paramagnetism.

The magnetic moments of **3a—d** in the solid state lie between 1.2 and 5.3 μ_B at 300 K and between 0.3 and 0.9 μ_B at 4 K. In this temperature range, **3e** is diamagnetic. The change in low spin-high spin equilibrium with temperature can be followed in solution by ^{31}P-NMR spectroscopy (Fig. 1). Optimized thermodynamic parameters ΔG^0, ΔH^0, and ΔS^0 for the low-spin→high-spin transition can be determined from the measurements if the following temperature-dependence of δ is assumed[4] (Table 1):

$$\delta = \frac{C}{T(1+e^{\Delta G/RT})} + \delta_{ls}$$

Table 1. Equilibrium constants and thermodynamic parameters for the low-spin→high-spin transition in **3a—d**.

		3a	3b	3c	3d
ΔH^0	[kJ/mol]	25.1	24.8	14.1	23.3
ΔS^0	[J/mol K]	69	73	56	66
ΔG^0_{300}	[kJ/mol]	4.4	2.9	−2.7	3.5
K_{300} =	[hs]/[ls]	0.17	0.31	2.95	0.25
high spin fraction [%] at 300 K		15	24	75	20

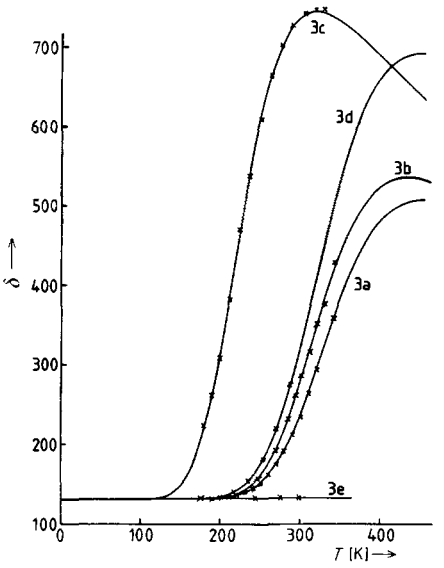

Fig. 1. Temperature dependence of the ^{31}P-NMR shift of **3a—e**, measured (×), and, in the case of **3a—d**, calculated using the parameters quoted in Table 1 (solvent: CD_2Cl_2/CD_3COCD_3).

The phosphinito complex **3e** is apparently diamagnetic over the whole temperature range under study. In contrast, in the case of the phosphito-complexes **3a—d** a temperature-dependent spin-equilibrium of the form $^5T_2(O_h) \rightleftharpoons {}^1A_1(O_h)$ at the central Co^{3+} is observed. The reason for this difference in behavior can be ascribed to the opposing inductive influences of the substituents R. Owing to the +I effect of the ethyl substituents, the two tripod ligands **1e** in the Co^{3+}-complex **3e** give rise to greater ligand-field splitting than the alkoxy-substituted ligands **1a—d** in **3a—d**. In the case of the phosphito complexes **3a—d** the high-spin/low-spin ratio increases markedly in the series R = OMe < OEt ≈ OBu ≪ O*i*Pr. This finding can be explained in terms of the increasing steric crowding of the ligands **1** in the Co^{3+}-complex **3**. The inter-ligand interactions due to this steric overcrowding lead to longer metal-donor atom bonds on going from **3a** to **3c**, and thus to diminishing ligand-field splitting[5]. This explanation is confirmed by the electronic spectra of the Co^{2+}-complexes **2a—d** and of the Ni^{2+}-complexes **4a—d**.

The magnetic measurements are consistent with the ligand-field spectra regarding the tripod ligands **1a—e**: The ligands **1a—d** are so weak and hard that an equilibrium exists between the d^6 high-spin and low-spin electron configuration in the Co^{3+}-complexes **3a—d**. The position of this equilibrium can be controlled to a large extent by the steric bulkiness of the alkoxy substituents. Ethyl substituents, on the other hand, make **1e** a distinctly stronger ligand than **1a—d**, for electronic reasons. The Co^{3+}-complex **3e** exists exclusively in the diamagnetic low-spin configuration. The steric and electronic effects of the substituents R in **1** thus allow a systematic fine tuning of ligand field strength in this novel class of oxygen ligands.

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[4] This equation implies that the high-spin and low-spin forms are in rapid equilibrium on the NMR time scale and can be described in terms of a Boltzmann distribution. Moreover, it is assumed that the chemical shift of the low-spin species δ_{ls} is temperature-independent and that the paramagnetism shows a temperature dependence according to the Curie law (see [2]).
[5] Depending upon the model under consideration the theoretically expected dependence is $\Delta \approx 1/r^{5-6}$. See, *e.g.*, H. L. Schläfer, G. Gliemann: *Einführung in die Ligandfeldtheorie*. Akademische Verlagsgesellschaft, Frankfurt/M. 1967, p. 66.

Chloro(phenoxy)carbene—A Nucleophilic Carbene having Temperature-Dependent Selectivity**

By *Wolfgang Brück* and *Heinz Dürr**

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

Carbenes normally react as electrophiles. Electron donor substituents or coupling of the carbene center to a $(4n+2)\pi$ system leads to nucleophilic carbenes. Positive reaction constants for the Hammett correlation were obtained for the addition of such intermediates to substituted isocyanates, whereas the Moss technique for the experimental determination of the m-parameter for carbene additions failed here[6,7]. The Moss-Mallon equation predicts that CF_2 (m = 1.48) has electrophilic, CH_3OCCl (m = 1.59) ambiphilic, and chloro(phenoxy)carbene **2** either electrophilic or ambiphilic character (**2**; $m_{calc.} = 1.49$).

We have now studied the selectivity of **2** using the styrene technique[5] and report on 1) the addition of **2** to styrenes, 2) the determination of reaction constants, and 3) their temperature dependence.

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α-Elimination of HCl from α,α-dichloroanisole **1** proceeds even at room temperature under phase transfer catalysis conditions with NaOH in presence of benzyltriethylammonium chloride (Fig. 1).

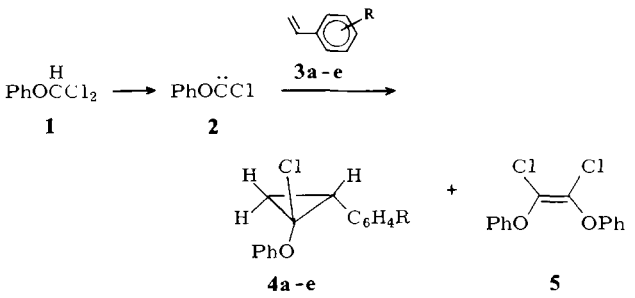

Fig. 1. **a**—**e**, see Table 1/2.

Reaction of **1** with the styrenes **3a**—**e** yields the cyclopropanes **4a**—**e** and the dimer **5** after chromatographic work-up. Products resulting from insertion into the olefin or aryl C—H bonds could not be detected.

The relative rate constants k_{rel} were determined by allowing **2** to react with styrene **3a** and a substituted styrene, **3b**—**e**, (molar ratio 1:5:5) at constant temperature; the values, which were obtained by gas chromatography, were evaluated using pseudo first order kinetics [eq. (1), simplified to (2)].

$$k_{rel} = \frac{k_B}{k_A} = \lg \frac{[B_0]/[B]}{[A_0][A]} \quad (1) \qquad k_{rel} = \frac{[B]}{[A]} \quad (2)$$

The selectivity of **2** is strongly temperature-dependent, and is consistent with the results of *Giese et al.*[13] for other carbenes. The reaction constants shown in Table 1/2 were obtained by plotting $\lg k_{rel}$ as a function of the Hammett σ-values (Fig. 2). The correlation coefficients lie between 0.98 and 0.99.

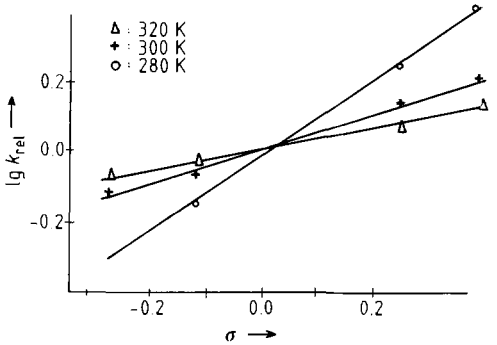

Fig. 2. Hammett correlation for the addition of **2** to styrenes **3**.

Table 1/2 (Selection). Yields [a] of cyclopropanes **4**, relative rate constants k_{rel} and ρ-values [k(**4a**, R = H) ≡ 1].

R		Yield 4 [%]	k_{rel} 280 K	300 K	320 K
p-OCH_3	*E*-**4b**	8	0.42	0.74	0.83
p-CH_3	*E*-**4c**	11	0.68	0.88	0.91
p-Cl	*E*-**4d**	6	1.77	1.12	1.02
m-Br	*E*- + *Z*-**4e**	7	2.39	1.53	1.24
ρ			1.11	0.40	0.23

[a] GC: 10% SE 30, Chromosorb PAW, 1.5 m, T = 190 °C.

The positive reaction constants prove that **2** is a nucleophilic carbene. According to MINDO/3 calculations on similar systems the electron density at the carbene center is certainly reduced by electron acceptor substituents, however, the resonance contribution of the lone pairs of electrons on oxygen produces an internal balancing of charge which leads to increased electron density in the p^0 orbital of the carbene. In contrast to chloro(phenyl)carbene[16a, 17], in **2** the temperature dependence of the selectivity is normal: *lowering* the temperature increases the *selectivity*.

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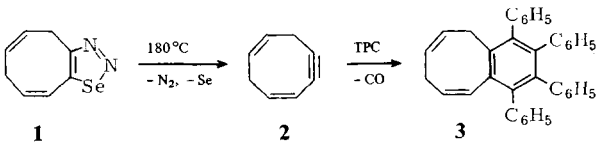
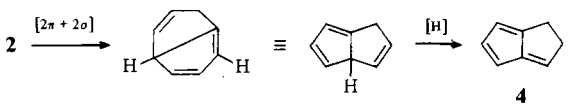
1,2-Dihydropentalene from 1,6-Cyclooctadien-3-yne**

By *Norbert Hanold, Thomas Molz,* and *Herbert Meier**

Cyclooctadienynes are highly strained hydrocarbons of the C_8H_8 series[1]. Their kinetic stability is essentially determined by thermal isomerizations on the C_8H_8 energy hypersurface[2]. Whereas 1,5-cyclooctadien-3-yne and 1,3-cyclooctadien-6-yne can be prepared in pure form, 1,3-cyclooctadien-5-yne is accessible only in solution. The latter, is also true for the 1,6-cyclooctadien-3-yne **2**, which can be obtained from the selenadiazole **1**[3].



In presence of tetraphenylcyclopentadienone (TPC), the trapping product **3** (m.p. = 217 °C) is formed in good yields. The preparation of pure **2** is thwarted by rapid isomerization to 1,2-dihydrocyclobutabenzene and styrene (22:78). On the other hand, under flash thermolysis conditions (450—640 °C, 0.3 torr) the 1,2-dihydropentalene **4**, first obtained by *Kaiser* and *Hafner*[6], is isolated as the main product.



The flash thermolysis of **2**, 1,3-cyclooctadien-5-yne, and 1,3-cyclooctadien-6-yne led to the following ratios of **4**,

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1,2-dihydrocyclobutabenzene, and styrene: 60:3:37, 0:9:91, and 0:0:100, respectively.

1,2-Dihydropentalene **4** was identified and characterized, *inter alia*, by the 100.62 MHz ^{13}C-NMR spectrum [δ = 23.1 (C-1), 40.7 (C-2), 111.9 (C-6), 114.5 (C-4), 142.2 (C-3, C-5), 151.3, 153.9 (C-3a, C-6a)].

In order to confirm the assignment of the ^{1}H-NMR signals, double resonance experiments were carried out at 400 MHz. The signals appearing at highest field are H-1 (δ = 2.66) and H-2 (3.10). The olefinic protons H-6, H-4, H-3, H-5 give highly split multiplets at δ = 5.95, 6.21, 6.83, and 6.90, respectively. The coupling behavior in this AA'BB'WXYZ system is very complex owing to long-distance couplings.

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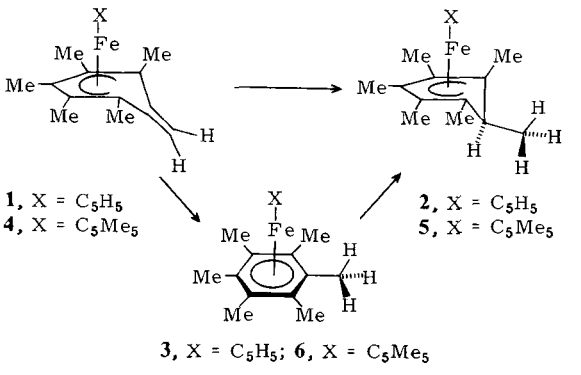
Cyclopentadienyl(peralkylarene) iron(I) Complexes as H Atom Reservoirs: Isolation of Semihydrogenated Species in the Pd/C Catalyzed Hydrogenation of Cyclopentadienyliron(II) Complexes of Exocyclic Olefins**

By *Pascal Michaud* and *Didier Astruc**

Concerted dihydrogen transfer in the heterogeneously catalyzed hydrogenation of olefins has been generally accepted for several decades[1a]. In some cases, however, the intermediacy of semihydrogenated species has been proposed on the basis of the stereochemistry of the reduction products, although they have never been isolated nor characterized spectroscopically[1b].

We report that stepwise double H atom transfer can occur when semihydrogenated species are stabilized.

The Fe^{II} complex $CpFe^{II}(\eta^5\text{-}C_6Me_5CH_2)$ **1**[2], in which neither of the olefinic C atoms is coordinated to the metal is hydrogenated by H_2/Pd/C to give **2** under ambient conditions in 2 h[2b,c]. The semihydrogenated Fe^I intermediate **3**[3] is a good candidate for the characterization of a stepwise double H atom transfer mechanism, since it bears one electron in an antibonding orbital of relatively low energy: **3** is stabilized by permethylation of the benzene ring. When **1** is hydrogenated (5% Pd/C, toluene, 20 °C, 1 bar H_2) the deep green color of **3** appears after 15 min; filtration and removal of the solvent *in vacuo* gives a black-green powder. The mass spectrum (*m/z* 283.114 M^+) and the Mössbauer doublet (IS = 0.73 mm s^{-1}; QS = 0.50 mm^{-1}) are characteristic of **3**[3]. From the Mössbauer absorption factors[4] of **1**, **2**, and **3** the relative abundance of **3** in the mixture is found to be 62.5%. The hydrogenation was also monitored by IR spectroscopy (decrease of the C=C band at 1660 cm^{-1} for **1** and the increase of the *exo*-stretching band at 2750 cm^{-1} for **2**). The maximum concentration of the Fe^I intermediate **3** is obtained after 20 min (Fig. 1). The second step, **3**→**2**, can also be effected starting with crystalline **3**[3b] under the same conditions: this is an oxidation of the metal $Fe^I \rightarrow Fe^{II}$ by H_2 whereas the first H atom transfer is a reduction $Fe^{II} \rightarrow Fe^I$.



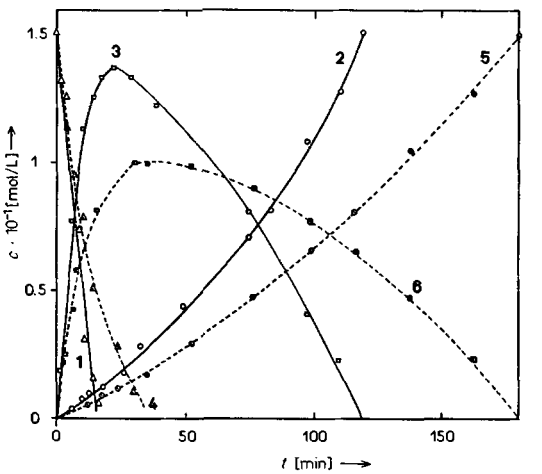


Fig. 1. Pd/C hydrogenation of **1** to **2** *via* **3** (—) and of **4** to **5** *via* **6** (---) at 20 °C; concentrations *c* followed by IR spectroscopy.

Like **1**, the pentamethylcyclopentadienyl analogue **4**[2c] is reduced to **5**[2c] *via* the intermediate **6**[3b] (Fig. 1). Finally the ethyl compound **7**[2c] reacts (5% Pd/C, 20 °C, 1 bar H_2, $t_{1/2}$ = 8 h) to give exclusively the d^7 complex **8**[3b] (Cp = η^5-C_5H_5).

$$CpFe^{II}(\eta^5\text{-}C_6Et_5CHMe) \underset{O_2(-H\cdot)}{\overset{H_2(+H\cdot)}{\rightleftharpoons}} CpFe^{I}(\eta^6\text{-}C_6Et_6)$$
7 **8**

Cleavage of H_2 upon hydrogenation can be homolytic or heterolytic[5], but in all known cases an H atom is transfered to a metal.

The complexes **3**, **6**, and **8** are not only reservoirs for electrons but also for H atoms. It should be noted that the exocyclic olefins **1**, **4**, and **7** are obtained from **3**, **6**, and **8** by H atom abstraction by O_2.

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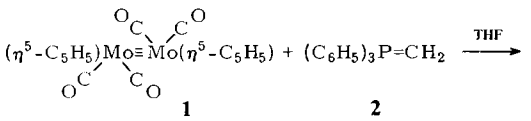
A μ_2-η^2-Styryl Complex by Reaction of $Cp_2Mo_2(CO)_4$ with the Wittig Reagent $(C_6H_5)_3P{=}CH_2$**

By *Klaus Endrich, Richard Korswagen, Thomas Zahn,* and *Manfred L. Ziegler*

Dedicated to Professor Georg Wittig on the occasion of his 85th birthday

$Cp_2Mo_2(CO)_4$ **1** reacts with nucleophiles as well as with electrophiles with formal addition to the MoMo triple bond[1]. Diphenyldiazomethane[2] and diazocyclopentadiene[3] also react with **1**, with formation of bridge complexes. In continuation of our studies on the reactivity of Wittig reagents towards organometallic substrates we have now carried out the reaction of **1** with the phosphorus ylide **2**, and, in accordance with the scheme,



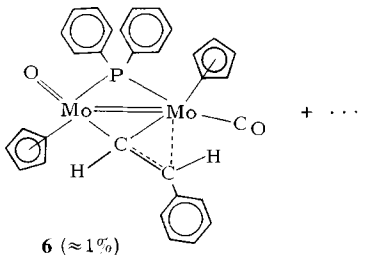
1 **2**

$(C_6H_5)_3P + CH_3(C_6H_5)_2P{=}O +$

3 (2%)

$[(\eta^5\text{-}C_5H_5)Mo(CO)_3]_2 + (\eta^5\text{-}C_5H_5)_2Mo_2(CO)_5[P(C_6H_5)_3] +$

4 (3%) **5** (10%)



6 (≈1%)

obtained the violet μ_2-η^2-styryl complex **6** as byproduct. This unusual compound was unequivocally characterized on the basis of IR, ^{1}H-NMR and mass spectra and by an X-ray structural analysis (Fig. 1).

6 is a doubly bridged Mo_2-complex with a diphenylphosphido bridge and an unsymmetrical (σ,π) η^2-styryl bridge. Both bridge-forming ligands are 3-electron donors, and, on the basis of the electron balance, a MoMo double bond must be present in **6**. Such a "degradation" of the MoMo triple bond in **1** to a double bond has so far not been reported in the literature; all other products would indicate presence of a MoMo single bond[1-3].

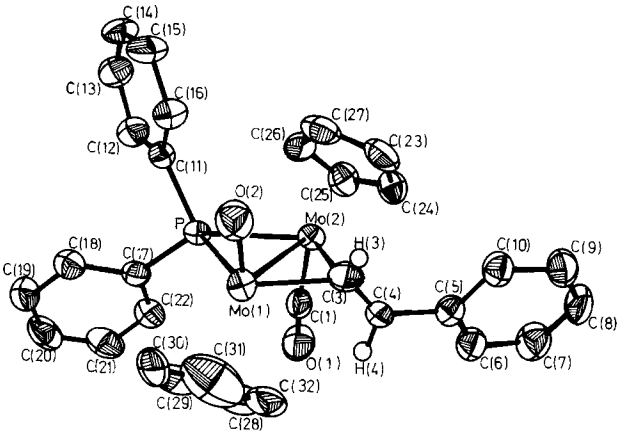


Fig. 1. Molecular structure of **6** in the crystal; the thermal ellipsoids correspond to a probability of 50%. Mo(1)—Mo(2) 288.5(1), Mo(1)—P 244.1(2), Mo(2)—P 234.9(2), Mo(1)—C(3) 205.7(9), Mo(2)—C(3) 215.8(10) pm. Further details about the crystal structure investigation can be obtained on request from the Fachinformationszentrum Energie-Physik-Mathematik, D-7514 Eggenstein-Leopoldshafen quoting Registry No. CSD 50256, the author, and the journal.

The spectroscopic data of **6** are consistent with the structural findings: Thus, the proton on the bridge carbon atom C(3), with $\delta = 9.91$, shows a chemical shift typical for μ-alkylidene complexes. The IR spectrum shows a band at 1820 cm^{-1} in the ν_{CO}-region, the ν_{MoO} bands appear at 910 cm^{-1}.

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Synthesis of α-Vinyl-*P,P'*-ethylenebis(diorganophosphanes)

By *Wolf Jürgen Richter**

We recently reported the synthesis of substituted vinylphosphiranes, prepared by allowing organodichlorophosphanes ($RPCl_2$) to react with magnesium-butadiene[1]. Diorganochlorophosphanes (R_2PCl) react with butadiene to give phospholenium salts[2]: we report here on the 1,2-addition of 2 equivalents of R_2PCl **1** to magnesium-butadiene **2** to afford the novel α-vinyl-*P,P'*-ethylenebis(diorganophosphanes) **3** (Table 1)[3].

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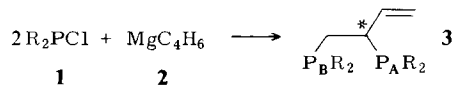

Table 1. Yields and selected physical data of the α-vinyl-*P,P'*-ethylene-bis(diorganophosphanes) **3a**—**3e**[3].

Compound	R	Yield [%]	B.p. [°C/torr]	^{31}P-NMR (C_6D_6) J_{PP} [Hz]	$\delta_{P(A)}$	$\delta_{P(B)}$
3a	C_6H_5	22	[a]	22.6	− 2.1	−20.4
3b	$CH(CH_3)_2$	58	96/0.01	26.6	+20.4	+ 1.8
3c	C_6H_{11}	64	145/0.01	26.9	+12.1	− 6.2
3d	$C(CH_3)_3$	28	140/0.01	30.8	+50.8	+22.5
3e [b]	Menthyl	52	[c]	16.4	−14.9	−29.6
				23.9	−17.9	−22.3

[a] Not determined. [b] Diastereometric mixture. [c] M.p. ≈ 173 °C.

Side reactions lead *inter alia* to formation of tetraorganodiphosphanes, particularly when aryl moieties are bonded to phosphanes. Thus, in the reaction of chlorodiphenylphosphane **1a** with **2**, apart from *ca.* 65% tetraphenyldiphosphane, only 22% of the bisphosphane **3a**, together with unidentified compounds were obtained.

The diorganochlorophosphanes **1b**—**1d** having branched alkyl moieties at phosphorus react to give the corresponding biphosphanes **3b**—**3d** in up to 64% yield, and only 3—5% of the respective tetraorganodiphosphanes. Chlorodimethylphosphane **1f** reacts with **2** to afford a diastereomeric mixture, in which the diastereomeric excess is only 16%. Even when less than the stoichiometric amount of **1** was used, monophosphino compounds could not be detected.

The ^{1}H-NMR and IR spectra of **3** indicate the presence of a vinyl group. The ^{31}P-NMR spectrum of **3** is particularly informative, since both phosphorus atoms have different substituents, thus giving rise to an AB system. The J_{PP} coupling constants and the chemical shifts are shown in Table 1; in this connection, the difference between the two diastereomeric menthyl compounds is notable. In the mass spectrum most compounds **3** exhibit the fragment ions at m/z $(M-R_2P)^{\oplus}$ as the base peak.

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[3] *Procedure:* A solution of chlorodiisopropylphosphane **1b** (8.7 g, 57 mmol) in 20 mL anhydrous toluene is added dropwise over 2 h to a solution of magnesium-butadiene **2** [4] (7.8 g, 35 mmol) in 60 mL anhydrous toluene at 0 °C. The mixture is stirred for 16 h, *ca.* 2.5 mL anhydrous dioxane added, and the precipitated $MgCl_2$·dioxane filtered off. After removal of the solvent using an oil pump, the residue is fractionated *in vacuo*. A colorless fraction of **3b** (4.7 g, 58%) is obtained at 96 °C.

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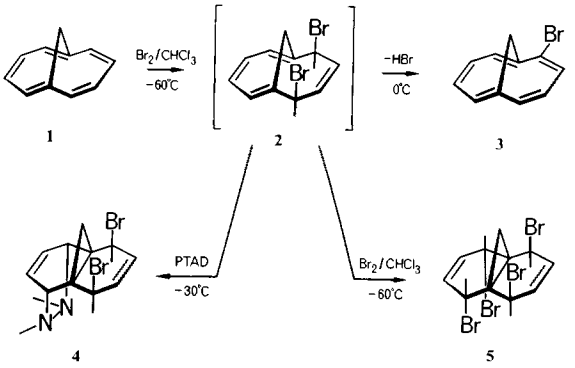
Stereochemistry of the Bromination of 1,6-Methano[10]annulene

By *Thomas Scholl, Johann Lex,* and *Emanuel Vogel**

The development of the chemistry of 1,6-methano[10]annulene **1** resulted, principally, *via* bromination reactions. In presence of either bromine at 0 °C or *N*-bromosuccinimide at 40 °C (in chloroform and dichloromethane, respectively), **1** is converted regioselectively and in high yield into 2-bromo-1,6-methano[10]annulene **3**. The findings of the bromination are consistent with those of extended Hückel and CNDO calculations[2].



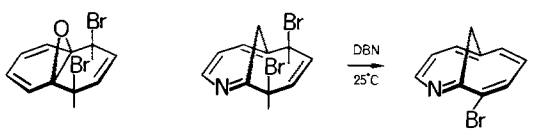
The substitution product **3** is highly probably formed *via* an addition-elimination mechanism, since in the reaction of **1** with bromine at −60 °C (in chloroform) a dibromo adduct (**2** or its isomer having reversed configuration of the bromine atoms), which is stable up to *ca.* −30 °C and results from a stereoselective *cis*-1,4-addition, can be detected by NMR spectroscopy. Upon warming to 0 °C the dibromo adduct is converted into **3**[1a].

Until now it was not known whether the bromine added to **1** in a *syn*- or *anti*-position relative to the CH_2-bridge. We report here on the solution to this interesting stereochemical problem.

In contrast to **1**, the parent hydrocarbon of **2**, 2,5-dihydro-1,6-methano[10]annulene, reacts very readily with dienophiles to form adducts derived from the norcaradiene valence tautomer[3]. In parallel to this, **2** could be trapped with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) at −30 °C (in chloroform) to yield the Diels-Alder adduct **4** possessing a cyclopropane ring. As indicated by the X-ray structural analysis, the bromine atoms in **4** are *syn*-oriented relative to the cyclopropane ring. This result therefore proves that the addition of bromine to **1** proceeds from the same side as the CH_2-bridge, although steric reasons would have led one to expect an attack from the opposite direction.

Renewed addition of bromine to **1** at −60 °C (in chloroform) also occurs in a *cis*-1,4-fashion to afford a tetrabromo adduct, which according to the results of previous ^{1}H-NMR investigations[1a] in conjunction with the identification of the dibromo adduct as **2**, must be the tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene derivative **5** with a *syn-anti*-configuration of the two pairs of *cis*-1,4-positioned bromine atoms relative to the cyclopropane ring. This was confirmed by X-ray structural analysis.

The isolation by *Effenberger et al.*[2] of a dibromodichloro adduct analogous to **5** in the low-temperature bromination of **1** in presence of benzyltriethylammonium chloride is viewed as proof that **2** and **5**, respectively, are not formed by synchronous addition of bromine but *via* an intermediate σ-complex.



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The same stereochemistry of bromination as observed for **1** could also be derived for 1,6-oxido[10]annulene. An X-ray structural analysis of the isolable dibromide **7**[1a] now indicated the *syn*-configuration of the two *cis*-1,4-positioned bromine atoms relative to the epoxide ring. Comparison of the NMR spectrum of the tetrabromo adduct[1a] with that of **5** suggests an analogous structure.

syn-Attack of bromine is apparently typical for 1,6-bridged[10]annulenes, since bromination of 2,7-methanoaza[10]annulene[4a] at −75 °C (in dichloromethane) leads to the labile bromo adduct **10**, which corresponds to **2** and **7** in the arrangement of the bromine atoms, and which upon standing, or more appropriately in presence of diazabicyclononene (DBN) in tetrahydrofuran (THF), undergoes regioselective dehydrohalogenation to yield the 3-bromo-2,7-methanoaza[10]annulene **11**[4b]. **10**, which did not afford a Diels-Alder adduct, could be subjected to an X-ray structural analysis despite its instability[4c].

The stereochemistry of the bromination **1** → **2** is interpreted in terms of MO theory in the following communication[5].

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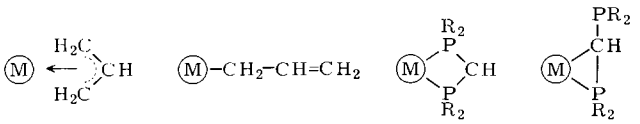
$Me_2PCHPMe_2^{\ominus}$ as Ambidentate Chelate Ligand**

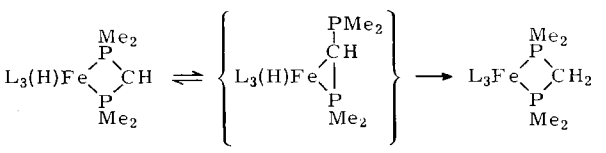
By *Hans Heinz Karsch**

Allyl transition-metal complexes are characterized by a special type of bonding isomerism (**A**, **B**).



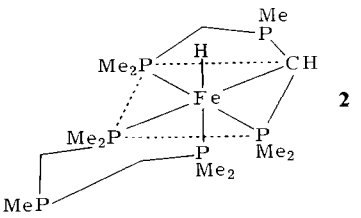
A **B** **C** **D**

In contrast, in mononuclear complexes of the "heteroallyl" anion $R_2PCHPR_2^{\ominus}$ only the form **C** (R = Ph) was previously known[1]. We consider the rearrangement **1a** → **1c** (L = PMe_3) as possible evidence for coordination of type **D** (R = Me)[2]. **1b** is, however, not detectable. Complex **2** is known to be coordinated according to type **D**[2], but the influence of the ring-strain in the bicycle is difficult to estimate.



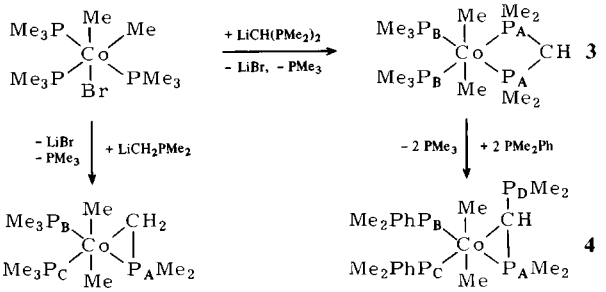
1a **1b** **1c**

We have now found an example in which a diphosphinomethanide complex of type **C** spontaneously rearranges to one of type **D**—without additional strain effects—as a result of only a slight change in the ligand periphery.



2

Complex **3** is present in solution as form **C**[3]. Substitution of the PMe_3 ligands in **3** by the sterically slightly more demanding PMe_2Ph leads to formation of **4**, with the "space-saving" configuration of type **D**[3,4]. This was confirmed by comparison with **5**, which also exhibits this structural element[3].



5 **3** **4**

The different mode of coordination of $R_2PCHPR_2^{\ominus}$ in **3** and **4** clearly indicates that the apparently slight energy difference considerably facilitates interconversion of the two coordination types, such as *e.g.* also in **1a** and **1b**. In this way, phosphorus and carbon in phosphinomethanides compete for complexed transition-metal centers just as for electrophilic main group compounds[5].

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[1] J.-M. Bassett, J. R. Mandl, H. Schmidbaur, *Chem. Ber. 113* (1980) 1145.
[2] H. H. Karsch, *Angew. Chem. 94* (1982) 322; *Angew. Chem. Int. Ed. Engl. 21* (1982) 311; H. H. Karsch, D. Neugebauer, *ibid. 94* (1982) 322; *21* (1982) 312.
[3] **3**: Orange crystals, m.p. = 95–97 °C (decomp.); MS: *m/z* 376 (M^+); ^{1}H-NMR ($C_6D_5CD_3$, +30 °C): $\delta P_ACH_3 = 1.29$ ($X_6AA'X'_6$ spin system), $\delta P_BCH_3 = 0.99$ ($X_6AA'X'_6$ spin system), $\delta CoCH_3 = -0.18$ tt [^3J(PCoH) = 6.8/8.3 Hz], δCH: assignment uncertain due to overlap of signals; ^{31}P{^{1}H}-NMR (36.43 MHz, −70 °C): AA'BB', $\delta P_A = -17.8$, $\delta P_B = +20.3$ [^2J(PP): AA' = 118 BB' = 56, AB = A'B' = 72, AB' = A'B = 220 Hz].—**4**: orange-brown crystals, m.p. = 95–99 °C (decomp.); MS: *m/z* 500 (M^+); ^{1}H-NMR ($C_6D_5CD_3$, +30 °C): $\delta P_ACH_3 = 1.51/1.45$, $\delta P_BCH_3 = 0.86/0.80$, $\delta P_CCH_3 = 0.54/0.45$, $\delta P_DCH_3 = 1.13/0.99$ [for symmetry reasons, doubled, broadened and, in part, superimposed doublets assigned from ^{31}P{^{1}H}, $\delta CoCH_3 = -0.35$ q/−0.80 q (^3J(PCoCH) = 8.0/7.6 Hz), δCoCH: as in **3**, ^{31}P{^{1}H}-NMR (36.43 MHz, −70 °C): $\delta P_A = -1.9$ dd, $\delta P_B = +34.4$ d, $\delta P_C = +32.3$ d, $\delta P_D = -53.9$ s [^2J(PP): AB = 205, AC = 46, BC < 6 Hz].—**5**: yellow crystals, m.p. 68–73 °C; MS: *m/z* 316 (M^+); ^{1}H-NMR ($C_6D_5CD_3$, +30 °C): $\delta P_ACH_3 = 0.95$ d,

$\delta P_B CH_3 = 0.92$ d, $\delta P_C CH_3 = 0.89$ d, $\delta CoCH_3 = -1.10$ dt [$^3_{cis}J$(PCoCH) = 8.9/7.8 Hz], $\delta CH_2 = -0.28$ dd [^2J(PCH) = 4.9, $^3_{cis}J$(PCoCH) = 7.1, $^3_{trans}J$(PCoCH) ≈ 0 Hz]; $^{31}P\{^1H\}$-NMR (36.43 MHz, −70 °C): $\delta P_A = -24.8$ dd, $\delta P_B = +30.5$ d, $\delta P_C = +26.1$ d [^2J(PP): AB = 208, AC = 43, BC < 6 Hz].

[4] A solution of $(Me_3P)_3Me_2CoBr$ (5 mmol) in tetrahydrofuran under an inert gas atmosphere is stirred for 3 h with $LiCH_2PMe_2$ or $LiCH(PMe_2)_2$ (5 mmol) at −40 °C. After removal of the solvent, the residue is taken up in 20 mL pentane, filtered, concentrated and cooled, whereupon 1.3 g **3** (69%) or 1.2 g **5** (70%) crystallize. Addition of 1.4 g PMe_2Ph to the reaction solution of **3** and analogous work-up yield 1.4 g **4** (56%).

[5] H. H. Karsch, *Z. Naturforsch. B 34* (1979) 1171, 1178, and literature cited therein.

Synthesis under High Pressure: Mannich Reaction of Ketones and Esters with Dichloromethane and Secondary Amines**

By *Kiyoshi Matsumoto**

The Mannich reaction, which is also involved in the biosynthesis of alkaloids, can be used to yield a variety of aminomethyl derivatives (Mannich bases), which, *e.g.* have many synthetic and pharmacological applications[1]. This reaction is plagued by some shortcomings, *e.g.* highly branched carbonyl compounds such as diethyl alkyl- or arylmalonates do not respond to the classical Mannich reaction, although several modifications have appeared[2]. In the course of studies of Michael addition under high pressure[3], we discovered that CH_2Cl_2 underwent a Menschutkin reaction with Et_3N to give $(ClCH_2)\overset{\oplus}{N}Et_3 \cdot Cl^{\ominus}$. This prompted us to investigate possible transformations using CH_2Cl_2 as a C_1 synthon[4], and we report the Mannich reaction of carbonyl compounds with CH_2Cl_2 and secondary amines at a pressure of 6—9 kbar[5] (Table 1).

Table 1. Yields and reaction conditions in the synthesis of Mannich Bases from carbonyl compounds, CH_2Cl_2 and Secondary Amines [a].

Substrate [b]	Amine	P [kbar]	T [°C]	t [h]	Isolated yield [%] [c]
$PhCOCH_3$	pyrrolidine	9	20	72	34 (81)
$PhCOCH_3$	piperidine	8	40	24	86 (93)
$PhCOCH_2CH_3$	$(Et)_2NH$	9	22	43	30 (51)
$PhCOCH_2CH_3$	$(i\text{-}Pr)_2NH$	8	40	39	14 (78) [d]
$PhCOCH(CH_3)_2$	pyrrolidine	9	40	48	56 (83) [e]
$PhCOCH(CH_3)_2$	$(i\text{-}Pr)_2NH$	9	48	72	14 (100)
$t\text{-}BuCOCH_3$	$(Et)_2NH$	6	40	48	30 (65) [f]
$CH_3CH(CO_2Et)_2$	$(Et)_2NH$	6	48	61	71 (86)
$PhCH(CO_2Et)_2$	$(Et)_2NH$	9	48	48	12 (44)
CH_3CO_2—nBu	pyrrolidine	9	48	72	32 [g]
cyclohexanone	$(Et)_2NH$	9	22	48	26 [h]

[a] The Mannich bases were characterized by elemental analyses and spectroscopic data (^{13}C- and ^1H-NMR, and IR). [b] Aminomethylation occurs at the C atom shown in italics (in the case of cyclohexanone in the α-position to the carbonyl group). [c] Yields of isolated products; in parentheses yields based upon consumed substrates. [d] With CH_2I_2 1.6% yield was obtained [4]. [e] CH_2ClI gave only a trace of the Mannich base. [f] CH_2Br_2 gave tar-like material with complete consumption of the substrate [4]. [g] According to the method described in [4], this reaction fails. [h] Higher temperatures (*e.g.* 40 °C) lead to bis-aminomethylation.

In most cases the present method affords virtually pure Mannich bases after simple work-up; distillation, which causes poor yields due to the thermal instability of the products was unnecessary.

Mannich bases which are highly sensitive to heat, *e.g.* from pinacolone are readily accessible. The relatively bulky phenyl isopropyl ketone reacts readily with a base, and even with diisopropylamine produces the expected Mannich base.

Diethyl methyl- and phenylmalonates also underwent the normal Mannich reaction.

Thus, the present procedure is considered to be a mild as well as powerful method of the aminomethylation, and gives good yields even with sterically demanding educts.

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CAS Registry numbers:
CH_2Cl_2, 75-09-2; $PhCOCH_3$, 98-86-2; $PhCOCH_2CH_3$, 93-55-0; $PhCOCH(CH_3)_2$, 611-70-1; t-$BuCOCH_3$, 75-97-8; $CH_3CH(CO_2Et)_2$, 609-08-5; $PhCH(CO_2Et)_2$, 83-13-6; $CH_3CO_2(CH_2)_3CH_3$, 123-86-4; $(Et)_2NH$, 109-89-7; $(i\text{-}Pr)_2NH$, 108-18-9; CH_2I_2, 75-11-6; CH_2ClI, 593-71-5; CH_2Br_2, 74-95-3; cyclohexanon, 108-94-1; pyrrolidin, 123-75-1; $PhCOCH_3$ pyrrolidine Mannich product, 94-39-3; $PhCOCH_2CH_3$ $(Et)_2NH$ Mannich product, 38847-75-5; $PhCOCH_2CH_3$ $(i\text{-}Pr)_2NH$ Mannich product, 83710-39-8; $PhCOCH(CH_3)_2$ pyrrolidine Mannich product, 35929-19-2; $PhCOCH(CH_3)_2$ $(i\text{-}Pr)_2NH$ Mannich product, 83710-40-1; tBuCOCH$_3$ $(Et)_2NH$ Mannich product, 3492-06-6; $CH_3CH(CO_2Et)_2$ $(Et)_2NH$ Mannich product, 80073-77-4; $PhCH(CO_2Et)_2$ $(Et)_2NH$ Mannich product, 83710-41-2; $CH_3CO_2(CH_2)_3CH_3$ pyrrolidine Mannich product, 59629-69-5; cyclohexanone $(Et)_2NH$ Mannich product, 37408-85-8.

[1] Reviews: F. F. Blick, *Org. React. 1* (1942) 303; H. Hellmann, G. Opitz: *α-Aminoalkylierung*, Verlag Chemie, Weinheim, 1960; M. Tramontini, *Synthesis 1973*, 703; K. Matsumoto, *Jikken Kagaku Koza* Vol. 14-III, Tokyo, Maruzen, 1978, p. 1373 ff.

[2] See *e.g.* J. Schreiber, H. Maag, N. Hashimoto, A. Eschenmoser, *Angew. Chem. 83* (1971) 355; *Angew. Chem. Int. Ed. Engl. 10* (1971) 330; T. A. Bryson, G. H. Bonitz, C. J. Reichel, R. E. Dardis, *J. Org. Chem. 45* (1980) 524.

[3] K. Matsumoto, *Angew. Chem. 92* (1980) 1046; *Angew. Chem. Int. Ed. Engl. 19* (1980) 1013; *93* (1981) 803; *20* (1981) 770.

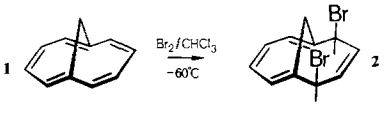
[4] The Mannich reaction using CH_2ClI: S. Miyano, A. Mori, H. Hokori, K. Ohta, H. Hashimoto, *Bull. Chem. Soc. Jpn. 55* (1982) 1331.

[5] *Experimental:* A mixture of the carbonyl compound (10 mmol), CH_2Cl_2 (20 mmol), and amine (30 mmol) is diluted with methanol in a 10 mL Teflon capsule which is stored for 24—72 h under high pressures (Table 1). The reaction mixture is diluted with 1 M HCl (100 mL) and extracted with several portions of hexane. The aqueous phase is made basic with NaOH, extracted with ether (20 mL × 3), washed with 2 M Na_2CO_3, brine, and water and then dried over $CaSO_4$. Evaporation of the solvent and unchanged amine under reduced pressure gives a virtually pure Mannich base.

MO Model for the Stereochemistry of Bromination of 1,6-Methano[10]annulene**

By *Rolf Gleiter**, *Michael C. Böhm*, and *Emanuel Vogel*

At low temperatures bromine adds to 1,6-methano[10]annulene **1** *syn* to the CH_2-bridge[1] to afford the labile dibromide **2**.



1 2

This result, which is surprising for stereochemical reasons, can be explained by π/σ interactions, which have

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Institut für Organische Chemie der Universität
Greinstrasse 4, D-5000 Köln 41 (Germany)

[**] This work was supported by the Fonds der Chemischen Industrie and BASF Aktiengesellschaft, Ludwigshafen.

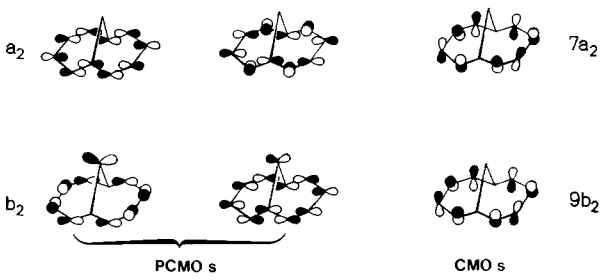

Fig. 1. Schematic representation of the most important precanonical MO's of **1** which interact with the π orbitals (left), as well as the resulting canonical π orbitals $7a_2$ and $9b_2$ (right).

been discussed for similar π/σ nonorthogonal systems[2]. Semiempirical MO calculations on **1** using a modified INDO method[3] predict a large σ/π interaction. A quantitative analysis according to ref.[4] indicates that each of the two high-lying π orbitals of the perimeter interacts considerably with two precanonical σ orbitals (PCMO's) (Fig. 1). The resulting canonical π orbitals (CMO's) $7a_2$ and $9b_2$[5] are also shown in Figure 1. The π/σ interaction causes rotation of the pπ atomic orbitals at the C(2)/C(5) and C(7)/C(10) centers.

Assuming that a bromine molecule approaches annulene **1** either parallel (**3a**) or perpendicular (**3b**) to the plane of the perimeter the antibonding interaction between the occupied levels of the halogen [for (**3a**) π and π*, for (**3b**) π* and σ] and $9b_2$ and $7a_2$ in *syn*-addition is smaller than that

in *anti*-addition. This is shown in Figure 2 for the approach parallel to the plane of the perimeter (**3a**). The main reason for the above mentioned difference is the smaller overlap[2b] between the π orbitals at the C(2)/C(5) or C(7)/C(10) centers of **1** and the corresponding orbitals of bromine in *syn*-addition compared to *anti*-addition. The rotation of the CMO's demonstrated in Figure 1 also occurs in the norcaradiene valence tautomer of **1**.

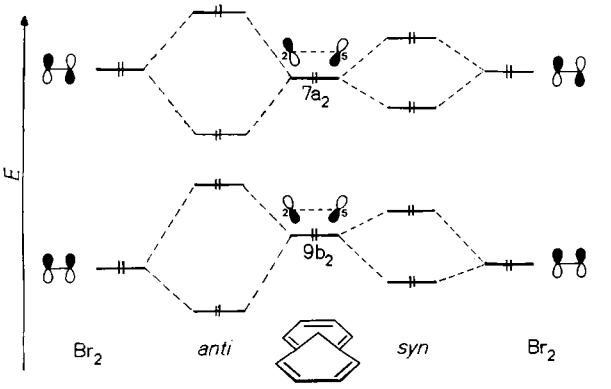

Fig. 2. Qualitative diagram for the interaction between the highest occupied molecular orbitals of Br_2 and the CMO's of **1** ($7a_2$ and $9b_2$) for *anti*- (left) and *syn*-addition (right), assuming that Br_2 approaches parallel to the plane of the perimeter (see **3a**).

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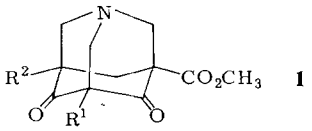
CAS Registry number:
1, 2443-46-1

[1] Th. Scholl, J. Lex, E. Vogel, *Angew. Chem. 94* (1982) 924; *Angew. Chem. Int. Ed. Engl. 21* (1982) 920.
[2] a) S. Inagaki, H. Fujimoto, K. Fukui, *J. Am. Chem. Soc. 98* (1976) 4054; b) L. A. Paquette, L. W. Hertel, R. Gleiter, M. C. Böhm, *ibid. 100* (1978) 6510; M. C. Böhm, R. V. C. Carr, R. Gleiter, L. A. Paquette, *ibid. 102* (1980) 7218; L. A. Paquette, F. Bellamy, M. C. Böhm, R. Gleiter, *J. Org. Chem. 45* (1980) 4913; c) K. Takahashi, K. Takase, T. Kagawa, *J. Am. Chem. Soc. 103* (1981) 1186; L. A. Paquette, P. Charumilind, *ibid. 104* (1982) 3749.
[3] M. C. Böhm, R. Gleiter, *Theor. Chim. Acta 59* (1981) 127.
[4] E. Heilbronner, A. Schmelzer, *Helv. Chim. Acta 58* (1975) 936.
[5] The calculated σ-contribution to both orbitals amounts to 10% ($7a_2$) and 30% ($9b_2$) respectively.

Synthesis of Specifically Substituted 1-Azaadamantanes

By *Nikolaus Risch** and *Wolfgang Saak*

1-Azaadamantanes[1] and related products are fascinating because of their interesting and, in part, surprising chemical and spectroscopic properties[2]. We have found a synthetic route, which for the first time provides a straightforward access to methyl 5,7-dialkyl-4,6-dioxo-1-azaadamantane-3-carboxylates **1** (Table 1), the first 1-azaadamantanes with completely C-substituted bridgehead atoms. The key step involves a triple Mannich reaction.



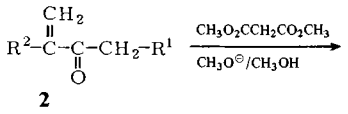
1

Table 1. Examples of Compounds **1** [a].

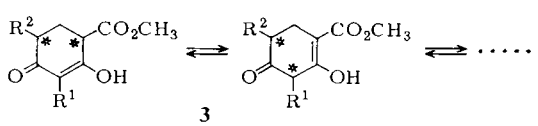
1	R^1	R^2	M.p. [°C]	Yield [%]
a	CH_3	CH_3	226	81
b	CH_3	C_2H_5	156	77
c	CH_3	n-C_8H_{17}	107	68
d	CH_3	$C_6H_5CH_2$—	192	70

[a] Spectroscopic characterization of **1a**, as example: ^{1}H-NMR (80 MHz, $CDCl_3$) 1.10 (s, 3H), 1.18 (s, 3H), 2.11 (AB, 2H), 3.08–3.66 (m, 6H), 3.80 (s, 3H). IR (KBr) 1739, 1723, 1692, 1269 cm^{-1}.

Michael addition and subsequent intramolecular Claisen condensation of the relatively easily available educts **2** and dimethyl malonate lead to the six-membered ring derivatives **3**, only a few of which have been described in the literature. A particular feature of **3** is the manifold possibilities of forming tautomers and stereoisomers.



2



3

We have found that refluxing **3** with 1,3,5,7-tetraazaadamantane (hexamethylenetetramine) in methanol/dichloromethane produces the 1-azaadamantane derivative **1** as

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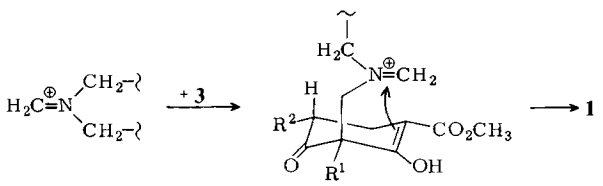
the sole product in high yield. Crystals were obtained after removal of the dichloromethane *in vacuo* and subsequent cooling, without further work-up. The structure has been confirmed by chemical and spectroscopic investigations[2].

We presume that the tetraazaadamantane framework is opened *via* an equilibrium with reactive intermediates of type **4**, which induce the Mannich-type reaction and form the intermediate **5**, which by analogy can react further. This formulation also accounts for the observation that **1** is the only product formed from each of the isomers **3**.



4 **5**

Compounds **1** are interesting, *inter alia*, as essential components of asymmetric catalysts, as models for reactions at fixed, sterically hindered systems, for solvolysis reactions[3], and for detailed spectroscopic investigations.

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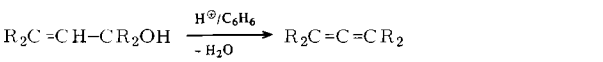
[1] H. Stetter, *Angew. Chem. 74* (1962) 361; *Angew. Chem. Int. Ed. Engl. 1* (1962) 286.
[2] N. Risch, unpublished results.
[3] C. A. Grob, M. Bolleter, W. Kunz, *Angew. Chem. 92* (1980) 734; *Angew. Chem. Int. Ed. Engl. 19* (1980) 708.

Tetra-*tert*-butylallene and Its Radical Cation**

By *Rudolf Bolze, Horst Eierdanz, Kaspar Schlüter, Werner Massa, Walter Grahn,* and *Armin Berndt**

Tetra-*tert*-butylallene **7** (m.p. = 43–44 °C) is the most highly sterically shielded and least chemically reactive allene derivative. It is formed as the sole product in the acid catalyzed dehydration of the readily accessible 1,1,3,3-tetra-*tert*-butylallyl alcohol **6**.



6 **7** R = *t*Bu

The steric shielding of the π system in **7** is clearly seen in the SCHAKAL plot[3] based on the results of an X-ray structure analysis (Fig. 1).

In accord with the large shielding, **7** displays practically no allene reactivity, and neither reacts with peroxy acids or ozone nor with chlorine or bromine, and is also inert to catalytic hydrogenation under pressure and to reaction with HI/phosphorus, or with strong aqueous acids. Only after being heated for several hours at temperatures above 100 °C with concentrated sulfuric acid does decomposition occur, which is observed as low as −60 °C with super acid.

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We attribute the low reactivity in addition reactions to the considerable steric hindrance, which affects all primary addition products. One-electron oxidation of **7** to generate the radical cation **10**, a reaction which is not accompanied by an increase in steric hindrance, can be smoothly achieved electrolytically or with $SbCl_5$ at −80 °C.

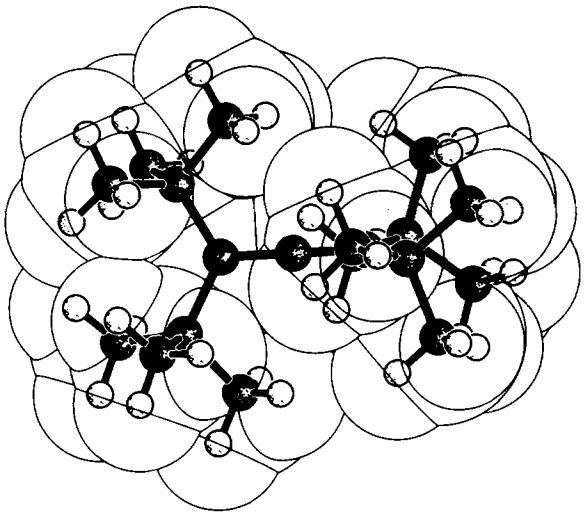
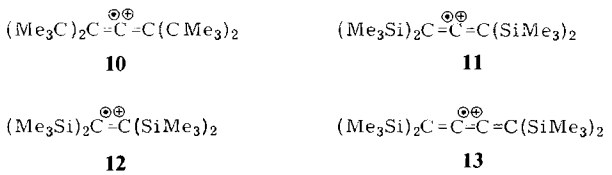


Fig. 1. SCHAKAL plot of the molecular structure of **7** (point symmetry 222 (D_2)) in the crystal. The space filling models are drawn with the van-der-Waals radii, and the ball-and-stick models arbitrarily with 1/5 of this value.

The radical cation **10** can be studied by ESR spectroscopy at temperatures up to −30 °C[6] in dichloromethane. The constitution of **10** is established by its ESR spectrum, which can be simulated using $a^H = 0.09$ mT for 36 equivalent H atoms and by the *g*-factor of 2.0028. The coupling constant of 0.09 mT for the sp^2-C atom, determined on **10** labeled with ^{13}C, precludes electronic structures in which either the unpaired electron or the positive charge is localized on the central sp-C atom. This establishes that the unpaired electron—and hence the positive charge—is distributed over all four p orbitals.

This electronic structure also occurs in the related radical cation **11**, which was generated by oxidation of tetrakis(trimethylsilyl)allene with $SbCl_5$ in CH_2Cl_2. The ESR spectrum of **11** can be simulated using $a^H = 0.022$ mT for 36 equivalent H atoms and $a^{Si} = 0.30$ mT for 4 equivalent ^{29}Si atoms (4.7% ^{29}Si).



10 **11**

12 **13**

The magnitude of the Si coupling constant in **11** is considerably smaller than that in **12** (1.775 mT)[11] and **13** (1.21 mT)[12], in which the unpaired electron occupies molecular orbitals consisting of only *two* p orbitals.

The small Si coupling constant in **11** is consistent with a distribution of the unpaired electron over all *four* p orbitals, since a^{Si} then contains a negative contribution arising from spin-polarization due to the spin density at the sp^2-C atoms (as in **12**) and a positive contribution arising from

hyperconjugation due to the spin density at the sp-C atom (as in **13**).

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The $HCo_3(CO)_9$-Catalyzed Olefin Isomerization**

By *Giuseppe Fachinetti** and *Annibale Stefani*

In reactions involving catalytic amounts of $HCo(CO)_4$ **1**, $Co_2(CO)_8$ **2** is usually always involved[1]. Recently we found that **1** and **2** exist in equilibrium with the trinuclear 46e cluster $HCo_3(CO)_9$ **3** [eq. (a)][6].

$$\underset{\mathbf{1}}{HCo(CO)_4} + \underset{\mathbf{2}}{Co_2(CO)_8} \rightleftarrows \underset{\mathbf{3}}{HCo_3(CO)_9} + 3CO \qquad (a)$$

We now communicate that **3** is directly involved in olefin isomerization promoted by compounds **1** and **2**. Double-bond shift occurs very rapidly in neat *n*-hexenes at 0 °C in presence of **3** (molar ratio *n*-hexenes : **3** = 5×10^3 : 1). In this respect 1-hexene isomerizes fastest and (*Z*)-2-hexene faster than (*E*)-2-hexene, as expected if formation of π-complexes is assumed to be the first step of the reaction (Table 1).

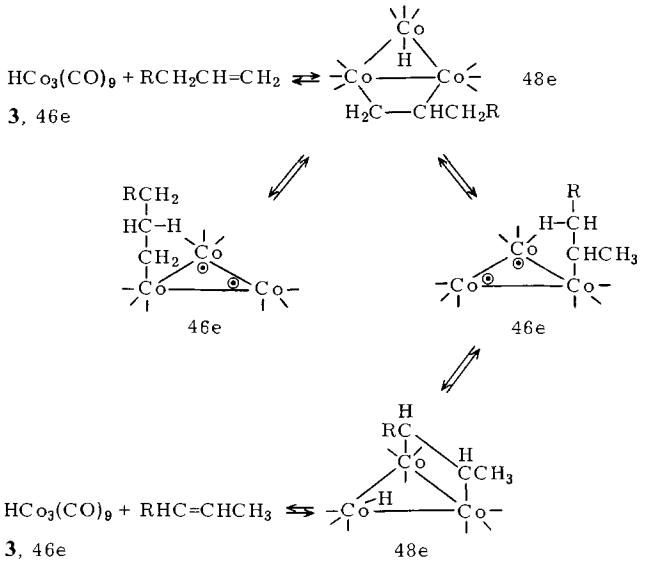
Table 1. $HCo_3(CO)_9$-catalyzed isomerization of neat *n*-hexenes at 0 °C (catalyst : substrate = $1 : 5 \times 10^3$).

Substrate	t [min]	Composition of the product mixture [a] 1-Hexene	(*Z*)-2-Hexene	(*E*)-2-Hexene	3-Hexene [b]
1-Hexene	*ca.* 0.5	3	30	59	8
(*Z*)-2-Hexene	3	<0.5	22	60	18
	18	<0.5	15	64	20
(*E*)-2-Hexene	3	<0.1	12	82	6
	10	<0.5	15	71	14
	40	<0.5	15	71	14
(*E*)-3-Hexene	3	<0.1	11	25	64
	10	<0.5	14	54	31
	40	<0.5	15	64	21

[a] Determined by gas chromatography. [b] Both (*Z*)- and (*E*)-3-hexene were always present in the mixture. The amount of (*Z*)-3-hexene in the mixture never exceeded 3%.

Experiments at $-35\,^{\circ}C$ in presence of **3** (molar ratio 2×10^3 : 1) show that (*Z*)- and (*E*)-2-hexenes are formed in equal amounts at 20% conversion within 3 min, despite the fact that the thermodynamic equilibrium lies very much in favor of (*E*)-2-hexene. When the reaction is carried out in cyclohexene, solvent and substrate compete in the first step of the reaction. The isomeric 2-hexenes can be obtained selectively at conversion rates up to 55% from 1-hexene.

Under these mild conditions neither **1** nor **2** show any catalytic activity, olefin isomerization being observed at higher concentrations of **1** in the presence of **2** and, at 0 °C, under an inert gas atmosphere. Since eq. (a) is operative under these conditions, the results suggest that cluster **3** might be the actual catalyst in the isomerization of olefins occurring in solutions containing **1** and **2**[11].



Scheme 2. Mechanism for olefin isomerization catalyzed by $HCo_3(CO)_9$.

It was previously demonstrated[8] that cobalt-catalyzed olefin isomerization occurs *via* consecutive metal-bonded hydrogen addition and elimination reactions. The observed C—H bond activations were explained in terms of 16e—18e additions of the mononuclear unsaturated hydridocarbonyl complex $HCo(CO)_3$ to the olefinic double bond, in accord with the hypothesis of *Heck* and *Breslow*[9]. Nevertheless, the trinuclear complex **3** could also react in this way (Scheme 2), whereby 46e—48e addition would occur[10], and the C—H bond activation would be promoted by two adjacent 17e cobalt atoms. The mechanism proposed in Scheme 2 is reminiscent of the Horiuti-Polanyi mechanism for the heterogeneously catalyzed olefin isomerization and, similar to heterogeneous catalysts, **3** is active even at $-50\,^{\circ}C$.

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CAS Registry numbers:
3, 71204-90-5; 1-hexene, 592-41-6; (*Z*)-2-hexene, 7688-21-3; (*E*)-2-hexene, 4050-45-7; (*E*)-3-hexene, 13269-52-8; (*Z*)-3-hexene, 7642-09-3; cyclohexene, 110-83-8.

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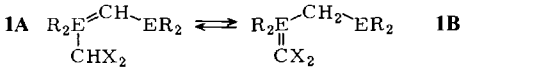
Stabilization of the Unstable Tautomers of Phosphino- and Arsino-Substituted Ylides by Coordination to Transition Metals**

By *Lothar Weber**, *Roland Boese*, and *Wolfgang Meyer*

Of the phosphino- and arsino-substituted ylides of type **1**, the tautomers **1A** and **1B** can be formulated, whereby the equilibrium for X = H at room temperature lies completely on the side of **1A**[1].



E = P, As; X = H, substituents capable of mesomerism
R = Alkyl, Aryl

Substituents X that are capable of mesomerism favor the tautomer **1B**, which can be fixed as complex ligand[2]. We have now been able to stabilize the tautomer **1B**, also when X = H, by coordination to transition metals. On reaction of the sulfur-ylide complexes **2**[9] or **6**[11] with the methylenebisphosphanes **4a—4c** and methylenebisarsane **4d** the unstable ylide tautomer is fixed as ligand to the transition metal. Formally, the $(CO)_4CrCH_2$ building block in **2** or **6** is transferred to **4a—4d** in a substitution reaction.

The ^{31}P-NMR spectra (200 MHz, 25 °C, $CDCl_3$, ext. H_3PO_4) of the yellow, briefly air-stable complexes **5a—5c** prove the presence of two different types of phosphorus atoms (**5a**: $\delta = 43.78$ (d), 65.47 (d), $J = 84$ Hz; **5b**: $\delta_A = 41.33$, $\delta_B = 43.09$, $J_{AB} = 81$ Hz; **5c**: $\delta = 90.58$ (d), 155.75 (d), $J = 105$ Hz). In **5d**, the methylene protons give rise to two singlets, in **5a—5c**, on the other hand, to two doublets of doublets. The X-ray structure analysis of **5d** (Fig. 1) confirms the presence of a five-membered metallacycle in envelope conformation (dihedral angle 36.7°).

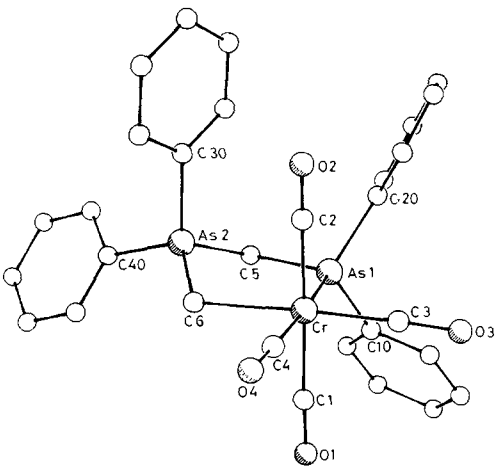
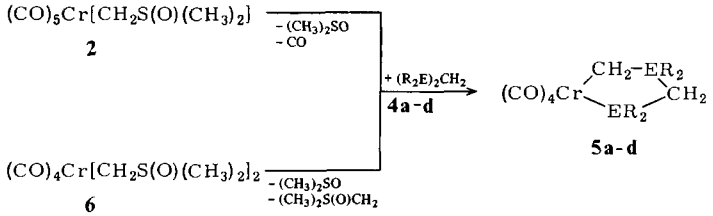


Fig. 1. Structure of the complex **5d** in the crystal. Monoclinic space group C2/c; $a = 2194.2(7)$, $b = 1418.5(4)$, $c = 2753.7(9)$ pm; $\beta = 138.87(2)°$; $V = 5.638(3) \times 10^9$ pm^3; $Z = 8$, $R = 0.035$.—Some selected bond lengths [pm] and angles [°]: Cr—As(1) 245.0(1), As(1)—C(5) 197.1(5), C(5)—As(2) 191.4(7), As(2)—C(6) 188.8(4), C(6)—Cr 222.1(6); CrAs(1)C(5) 109.8(2), As(1)C(5)As(2) 106.3(2), C(5)As(2)C(6) 107.6(3), As(2)C(6)Cr 113.6(2), C(6)CrAs(1) 88.1(1). Further details of the crystal structure investigation can be obtained on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2 (Germany), quoting CSD 50289, name of author, and full citation of Journal.



4, 5	a	b	c	d
ER_2	PPh_2	$P(CH_3)_2$[12a]	$P[N(CH_3)_2]_2$[12b]	$AsPh_2$

The free ylide ligands of the complexes **5c** and **5d** were hitherto completely unknown. The method described here is thus a general route to complexes with unstable ylide ligands of the type **1B**.

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Synthesis of an Octasaccharide of the Basic Sequence of *N*-Glycoproteins**

By *Hans Paulsen** and *Rolf Lebuhn*

The oligosaccharide chain **9** is a basic sequence present as a building block in numerous *N*-glycoproteins[1], and is bonded at the reducing end to L-asparagine *via* a glucosamine moiety. Both lactosamine antennae having the nonreducing end groups are usually occupied by *N*-acetylneuraminic acids[1].

Until recently, the β-D-(1→4)-mannoside bond to the glucosamine in **9** could not be synthesized directly. Using a silver silicate catalyst[2] we recently were able to prepare saccharides **2** and **6**[3], which were required as educts for the oligosaccharides **5** and **9**.

Trisaccharide **3**, which is obtained from **2** (Scheme 1), can be selectively coupled with the lactosamine bromide **1**[4] in presence of silver trifluoromethanesulfonate (Ag-triflate, collidine, −40 °C) to afford the pentasaccharide **4** (75%, $[\alpha]_D^{20}$ −9.7, $c = 1.2$ in $CHCl_3$) with the desired β-D-glycosidic linkage. **4** could be deblocked as follows: Firstly it is deallylated (70%) with $PdCl_2$/AcOH/NaOAc. Deacetylation, hydrazine cleavage of the phthalimido group, acetylation, and subsequent hydrogenolytic cleavage of the benzyl groups, as well as reacetylation led to a to-

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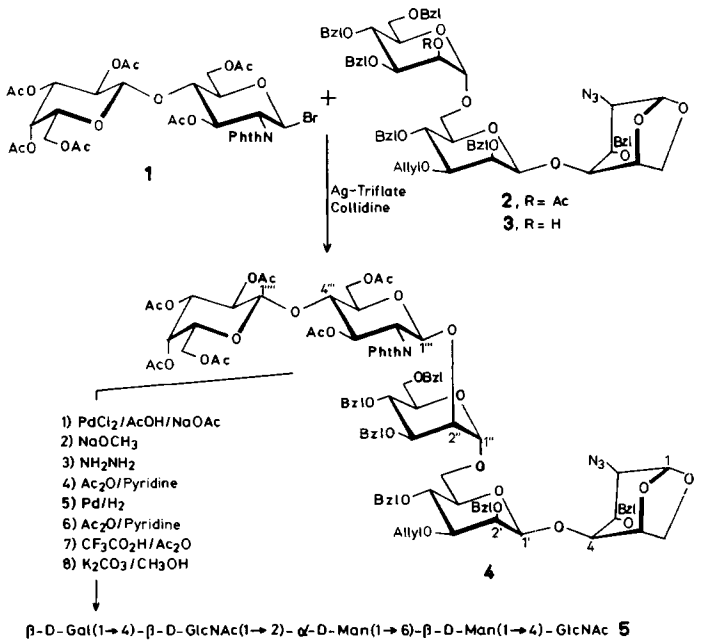
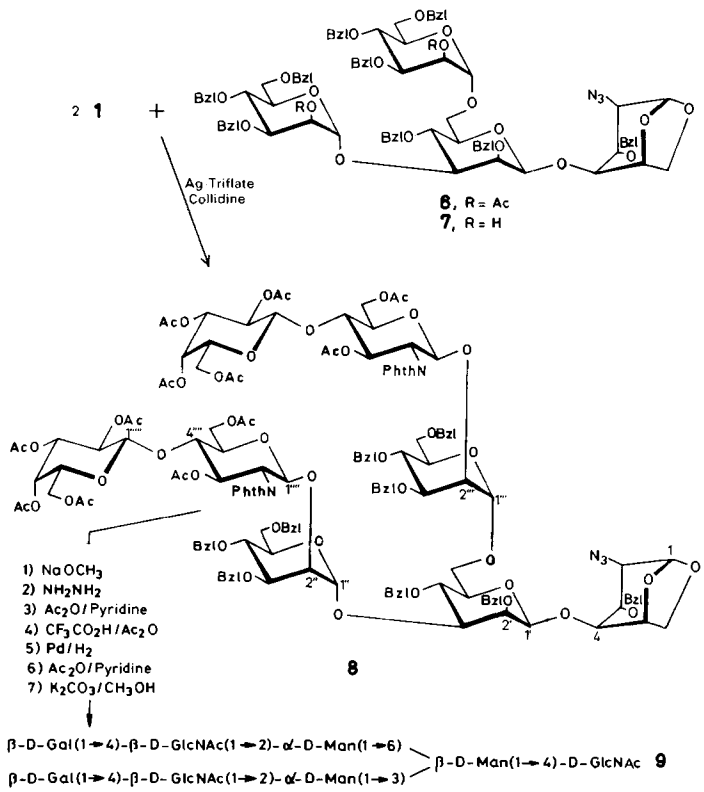
[**] Oligosaccharide Building Blocks, Part 42.—Part 41: H. Paulsen, M. Paal, *Carbohydr. Res.*, in press.



Scheme 1. Phth = phthaloyl.

tally acetylated compound (56%), which still only contains the 1,6-anhydro ring at the reducing moiety. This can be opened with CF_3CO_2H/Ac_2O (65%), and subsequent deacetylation with K_2CO_3/CH_3OH at 0 °C affords the free saccharide **5**[5] (90%, $[\alpha]_D^{20}$ +6.0, $c = 0.5$ in H_2O).

Tetrasaccharide **7**, which is obtained from **6**, reacts with **1** (molar ratio 1:2, Scheme 2) under the same conditions as the reaction of **1** with **3**. The octasaccharide **8** (70%, $[\alpha]_D^{20}$ −8.0, $c = 1.1$ in $CHCl_3$) is formed *via* stereoselective



Scheme 2. Phth = phthaloyl.

coupling of two β-D-glycoside bonds, and can be deblocked in three steps: After deacetylation, cleavage of the phthalimido group by hydrazine and reacetylation (77%) in the first step, follows 1,6-anhydro ring-opening, cleavage of the benzyl ether groups and reduction of the azido group by hydrogenation, as well as reacetylation (40%) in the second. Finally, the product is deacetylated by K_2CO_3 in methanol at 0 °C to afford the glycoprotein building block **9**[5] (90%, $[\alpha]_D^{20}$ +1.8, $c = 1.0$ in H_2O). The reducing glucosamine moiety is not converted into the *manno*-isomer under these conditions, which otherwise readily occurs in alkaline deacetylations of similar groups. The structure and linkage of all the oligosaccharides prepared were determined by analysis of the 400 MHz, ^{1}H-NMR spectra (in part, 2D spectra).

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[5] 400 MHz, ^{1}H-NMR data (selection, relative to HOD, $\delta = 4.64$, solvent D_2O): **5** (α-D-anomer). $\delta = 5.07$ (1-H), 4.6 (1′-H), 4.78 (1″-H), 4.43 (1‴-H), 4.32 (1⁗-H), 3.94 (2′-H), 3.96 (2″-H).—**9** (α-D-anomer): $\delta = 5.08$ (1-H), 4.6 (1′-H), 4.98 (1″-H), 4.80 (1‴-H), 4.44 (1⁗-H), 4.33 (1⁗′-H) (the second lactosamine moiety exhibits the same chemical shift for the two corresponding anomeric protons). 4.12 (2′-H), 4.05 (2″-H), 3.98 (2‴-H).

Synthesis of Trisaccharide Moieties from *N*-Acetylneuraminic Acid and *N*-Acetyllactosamine

By *Hans Paulsen** and *Holger Tietz*

Glycoproteins bound to L-asparagine by an *N*-glycosidic linkage contain a pentasaccharide core structure having a branched end section consisting of three mannoses. In the lactosamine type, lactosamine antennae carrying terminal α-D-(2→6)-glycosidic *N*-acetyl-D-neuraminic acid (NANA) are bonded there. We have now been able to synthesize the trisaccharide α-D-NANA(2→6)-β-D-Gal(1→4)-D-GlcNAC **11**, which is present as a functional terminal group in numerous glycoproteins.

Previous glycoside syntheses using neuraminic acid have caused severe problems[1]. We have studied the reactions of the chloride **7** and of the corresponding bromide, prepared by reaction of an acetylated *N*-acetylneuraminic acid ester with $TiCl_4$ or $TiBr_4$ under anhydrous conditions[2], in presence of numerous catalysts. With the bromide, predominantly elimination reaction occurs; only highly reactive monosaccharides having 6-OH groups react with **7** in presence of silver catalysts to afford disaccharides having α-D-glycosidic linkages. In compounds having less reactive OH groups, eliminations can be repressed by using $Hg(CN)_2/HgBr_2$ as catalyst; by this means disaccharides can be obtained in good yields, although, as a mixture of anomers. These conditions also proved to be suitable for a trisaccharide synthesis.

Bromide **1**[3] reacts with benzyl alcohol in presence of silver silicate[2] to give the benzyl glycoside **2**. After deacet-

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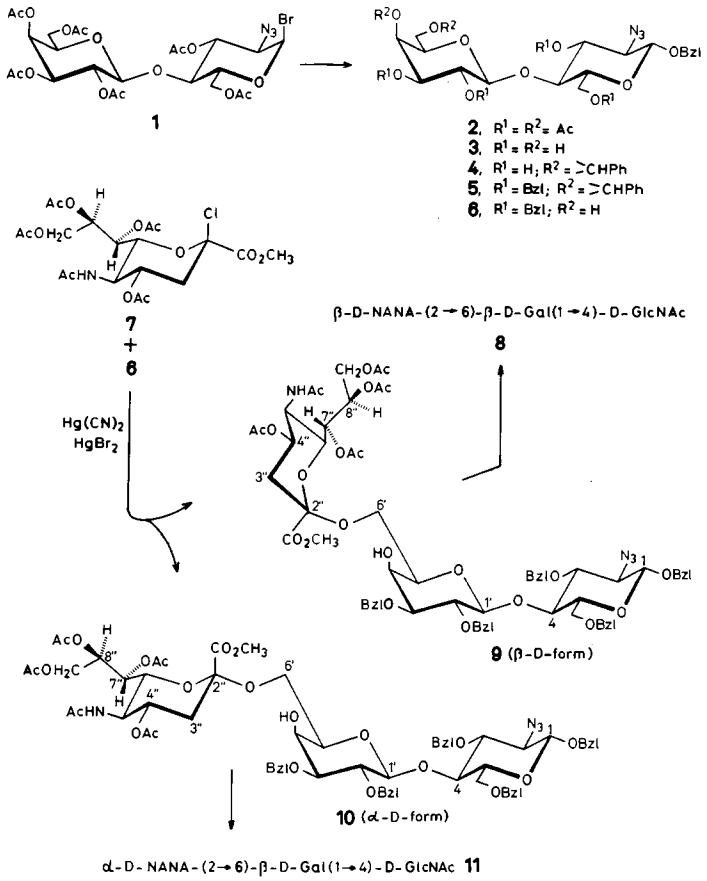
ylation to **3** this is converted by benzaldehyde dimethyl acetal into **4**, which after benzylation with benzyl bromide affords **5**. Subsequent acid hydrolysis furnishes **6**, which



can be used directly for glycoside synthesis, since 6′-OH is considerably more reactive than 4′-OH. **7** reacts with **6** in presence of $Hg(CN)_2/HgBr_2$ (3:1) in dichloromethane (20 °C, 3 d) to give the glycosides **9** and **10** (molar ratio 1:1) in approximately 50% yield. Column chromatography (chloroform/methanol) of the mixture results in isolation of 20% α-D-form **10** ($[\alpha]_D^{27}$ −12.8, $c=1.0$ in CH_2Cl_2) and 20% β-D-form **9** ($[\alpha]_D^{27}$ −4.0, $c=1.0$ in CH_2Cl_2). In order to deblock **10**, the N_3 group is first reduced by H_2S to the NH_2 group (62%), and both NH_2 and 4′-OH groups are subsequently acetylated (71%). The *O*-acetyl groups can then be cleaved using catalytic amounts of sodium methoxide in methanol and the methyl ester cleaved by NaOH (99%). Finally, the benzyl ethers are cleaved by hydrogenolysis leading to the free trisaccharide **11** ($[\alpha]_D^{26}$ −0.7, $c=1.0$ in H_2O)[4]. The β-D-form **9** can be analogously deblocked to afford the trisaccharide **8** ($[\alpha]_D^{27}$ −3.5, $c=1.0$ in H_2O)[4].

The assignment of the anomers was performed by comparison of the ^{1}H-NMR spectra of **8** and **11**. In the α-D-form **11**, the signal of 3″-H_e at $\delta=2.56$ (in D_2O) is characteristically[5] shifted to low field (3″-H_e of **8**: $\delta=2.31$). However, this rule does not apply to blocked *N*-acetylneuraminic acid oligosaccharides. Here we can state a new assignment rule for the case when the *N*-acetylneuraminic acid moiety is completely acetylated. In **10** and **9**, and in all intermediates the signal of 4″-H in the α-form at $\delta=4.89-4.93$ lies at higher field than in the β-form (4″-H, $\delta=5.68-5.81$). Furthermore, the $J_{7,8}$ coupling of 6.2—8.2 Hz in all the α-forms is large, and in contrast that in the β-forms of 2.4—2.6 Hz small, which suggests different conformations in the side chains.

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[4] 400 MHz ^{1}H-NMR in D_2O (relative to acetone, $\delta=2.12$): **8** (α-D-anomer): $\delta=5.11$ (1-H), 4.38 (1′-H), 2.31 (3″-H_e), 1.59 (3″-H_a), 1.93, 1.94 (N—Ac).— **11** (α-D-anomer): $\delta=5.01$ (1-H), 4.35 (1′-H), 2.56 (3″-H_e), 1.65 (3″-H_a), 1.93, 1.96 (N—Ac).
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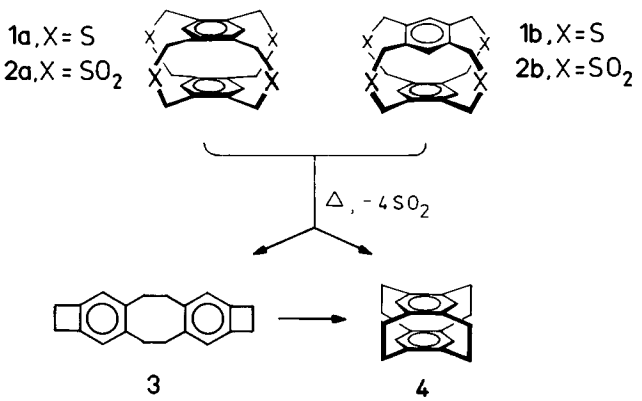
Novel Facile Synthesis of Multiply *ortho*-Bridged Phane-Hydrocarbons and of Dihydrocyclobutabenzenes

By *Brigitte Klieser* and *Fritz Vögtle**

We have now found that the cesium-catalyzed sulfide-cyclization recently developed by us enabled the one-step synthesis of multiply *ortho*-bridged benzene rings[1], *e.g.* of **1**; following on from that we have now succeeded by sulfone pyrolysis in synthesizing multiply 1,2-bracketed phane-hydrocarbons in a few simple steps, and—surprisingly—also of bridged dihydrocyclobutabenzenes. Multiply *ortho*-bridged phanes, unlike their *meta*-bridged analogs[3], were hitherto not accessible from sulfones[2].

Pyrolysis (600 °C/0.005 torr) of the mixture of sulfones **2a**, **b** (sublimation temp. 550 °C) obtainable from the mixture of the tetrasulfides **1a**, **b**[1], does not yield the desired fourfold bracketed phane **4**[4], but the doubly bridged 1,2-dihydrocyclobutabenzene **3**. The ^{1}H-NMR data of **3**[5] and **4**[4] are in complete accord with those quoted in the literature.



On pyrolysis of **2** at higher temperature (750 °C/0.15 torr; sublimation temperature 700 °C), however, we were able to isolate a 1:2 mixture of **3** and **4** in *ca.* 40% yield (unequivocal identification from ^{1}H-NMR signals and mass spectra).

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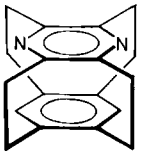
Our experimental findings that 1,2,4,5,7,8,10,11-octahydrobiscyclobuta[4,5]benzo[1,2-*a*:1′,2′-*e*]cyclooctene **3** is formed initially, and not the [2.2.2.2]cyclophane **4**, is very interesting, because **3** occurs as intermediate in the multistep synthesis of **4**[5], and **4** has already been obtained by thermolysis of **3**.

The novel synthetic route *via* an "ortho-sulfone pyrolysis" not only offers the advantage of a small number of rapid and simple steps, but also enables synthesis of dihydrocyclobutabenzene intermediates such as **3**, which are thus also conveniently accessible for other reactions. Furthermore, numerous unsymmetric phane-hydrocarbons such as the pyrazinobenzophane **5** should now be accessible in an analogous way from the corresponding unsym-



5

metrical sulfones, whereas previous methods were restricted to symmetrical compounds of type **3** and **4**. Fivefold and sixfold bracketed arenes—e.g. superphanes—including the corresponding dihydrocyclobutabenzene intermediates, should also be obtainable by this novel combination of cesium-catalyzed sulfide cyclization[1] and *ortho*-sulfone pyrolysis.

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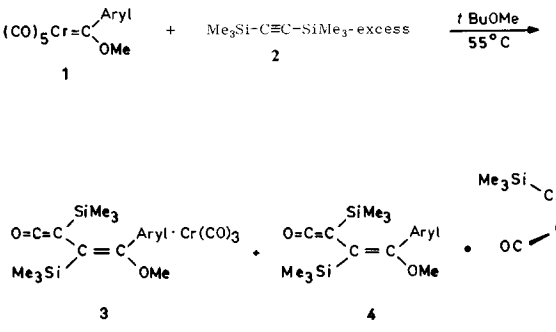
Bis[bis(trimethylsilyl)acetylene]dicarbonylchromium**

By *Karl Heinz Dötz** and *Jochen Mühlemeier*

Pentacarbonyl[aryl(methoxy)carbene]chromium complexes **1** react with equimolar amounts of bis(trimethylsilyl)acetylene **2** to give the metal-coordinated vinylketenes **3**, which can be formally described as products of a head-to-tail addition of the carbene and a carbonyl ligand to the alkyne[4]. In contrast, if the reaction is carried out with an excess of alkyne (*e.g.* in the ratio **1** : **2** = 1 : 2.2) in *tert*-butyl methyl ether, then, on heating, the uncoordinated vinylketene **4** and the title compound **5** are also obtained.

The deep-violet complex **5**, which is moderately sensitive to light and extremely sensitive to oxidation, was char-



Aryl = p-C_6H_4-R (R = H, Me, OMe, CF_3)

acterized by total analysis and by spectroscopic methods[5] [IR: ν(C=O) 1965, 1904 cm^{-1} (*n*-hexane), ν(C≡C) 1705 cm^{-1} (Nujol); ^{1}H-NMR: $\delta = 0.28$; MS: $m/z = 448$ (M^+), 392 ($M^+ - 2CO$), 222 ($M^+ - 2CO$—Me_3Si—C≡C—$SiMe_3$). In solution, bis(trimethylsilyl)acetylene is slowly cleaved from the complex if not kept in the dark, thus ruling out coupling of the alkyne ligands in the complex. Information about the coordination of the alkyne ligands is provided, in particular, by the ^{13}C-NMR spectrum: The signal of the C-atoms of the two CO-ligands appears at $\delta = 258.9$, that of the alkyne C-atoms at $\delta = 197.8$; such downfield shifts (free alkyne: $\delta = 115.4$) are regarded as a criterion for the alkynes functioning as four-electron ligands[6], thus leading to the noble gas configuration of the chromium in **5**. In contrast, the ^{29}Si chemical shift ($\delta = -7.4$) is unsuited for investigation of the electron-donor capability of the alkyne, as is revealed on comparison with the two-electron alkyne ligand in $(CO)_4Fe(Me_3Si—C≡C—SiMe_3)$ ($\delta = -8.5$)[9].

The bis(alkyne)dicarbonyl complex **5** constitutes the first satisfactorily characterized ternary alkyne-carbonyl compound of chromium, after the synthesis of the tris(alkyne)carbonyl complexes of molybdenum and tungsten could so far not be extended to the lightest homologue.

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Coordinatively Unsaturated Trinuclear Molybdenum-Sulfur Cluster Chelates with Dithiophosphinato Bridge

By *Helmut Keck, Wilhelm Kuchen**, *Jürgen Mathow*, and *Hartmut Wunderlich*

We have found that by allowing Mo_3S_7-cluster dithiophosphinates **1**[1] to react with triphenylphosphane partial

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desulfurization occurs leading to the coordinatively unsaturated, diamagnetic nonelectrolytes **2**.

$$[Mo_3S_7(R_2PS_2)_3]^+[R_2PS_2]^- \underset{+S_8 \text{ or } +(R_2PS_2)_2}{\overset{+R_2^1P:\,-R_2^1PS}{\rightleftharpoons}} [Mo_3S_4(R_2PS_2)_4] \quad (1)$$

1 **2**

1a, **2a**: R = Et; **1b**, **2b**: R = *n*Pr, R′ = Ph

Consistent with this structure (Fig. 1), the $^{31}P\{^1H\}$-NMR spectrum of **2a** exhibits three resonances in the intensity ratio 1 : 2 : 1 (0.03 M in CH_2Cl_2; $\delta_P = 123.2$, 114.8, and 83.7, rel. to 85% H_3PO_4) and the FD-mass spectrum the molecular ion ($[M]^+$, *m/z* 1034, ref. to ^{98}Mo).

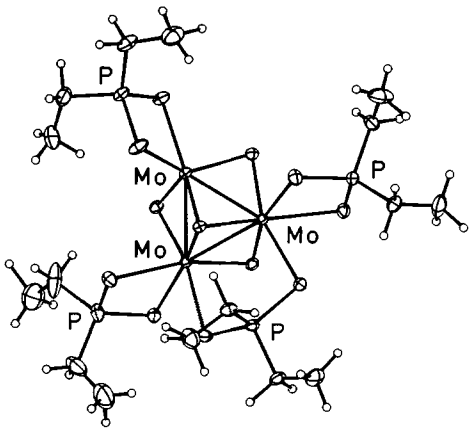

Fig. 1. Structure of the molybdenum(IV) cluster **2a** in the crystal.

The cluster contains the central unit Mo_3S_4[2–4]. As in **1a**, each of the Mo atoms, which form a triangle, is chelated by a dithiophosphinate moiety and capped trigonal-pyramidally by a sulfur atom. However, instead of the bridging S_2^{2-} ligands, single sulfide bridges now occur. Two of the Mo atoms are additionally linked to each other *via* a dithiophosphinato bridge, and hence sulfur fulfills four different bonding functions in the molecule. The formal oxidation state of the metal atoms in **2a** is the same as that in **1a**. However, in contrast to all other trinuclear MoS clusters the coordination number of the three Mo atoms in cluster **2a** is different: this is seven for one Mo atom and eight for the other two Mo atoms. In consequence, the coordinatively unsaturated compounds **2** can add, *e.g.* pyridine, to form $[Mo_3S_4(R_2PS_2)_4py]$ **3** (**3a**: R = Et; **3b**: R = *n*Pr) which upon heating is quantitatively released to give **2** again. The different coordination state in **3** is expressed *inter alia* by a distinct high-field shift of the resonances in the $^{31}P\{^1H\}$-NMR spectrum. Hence, **3a** also displays three resonances in the intensity ratio 1 : 2 : 1, however, at $\delta_P = 116.6$, 114.1, and 80.9 (0.03 M in CH_2Cl_2). As expected, the resonance of the chelate ligand bonded to the originally coordinatively unsaturated molybdenum atom is most strongly influenced: $\Delta\delta_P = 6.6$ ppm, relative to 0.7 and 2.8 ppm. Analogous situations are found when the resonances of **2b** and **3b** are compared.

Clusters **2** react with S_8 or $R_2P(S)S_2P(S)R_2$ (R = Et, *n*Pr) as sulfur donor to re-form **1**. Thus, reaction (1) reflects the redox process

$$S_2^{2-} \rightleftharpoons S + S^{2-}$$

The Mo_3 triangular plane remains intact both in the coordinative saturation of **2** and in reaction (1).

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1a, 79594-15-3; **1b**, 79594-18-6; **2a**, 83664-61-3; **2b**, 83664-62-4; **3a**, 83664-63-5; **3b**, 83664-64-6; Ph_3P, 603-35-0.

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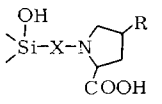
Chiral Silica Packings with L-Proline or L-Hydroxyproline Bonded *via* Alkyl or Alkylbenzyl Chains for the Separation of the Enantiomers of α-Amino Acids by HPLC

By *Panayiotis Roumeliotis, Klaus K. Unger*, Alexandre A. Kurganov,* and *Vadim A. Davankov*

The separation of enantiomers by means of column liquid chromatography has been the subject of numerous reports[1]. A favorite way of obtaining enantioselective supports consists in covalently bonding optically active ligands *via* a spacer to the surface of silica[2–4].

We synthesized silicon compounds of the type $(EtO)_3Si$—X-L-proline and $(EtO)_3Si$—X-L-hydroxyproline, which on reaction with LiChrosorb Si 100 ($d_p = 10$ μm; Merck) yielded chiral silica packings **1**–**4**.



1, X = $-CH_2-$
2, X = $-(CH_2)_3-$
3, X = $-(CH_2)_8-$
4, X = $-(CH_2)_2-C_6H_4-CH_2-$

a, R = H; **b**, R = OH

The concentration of surface functional groups amounted to 3—4 μmol/m^2. The supports were packed in columns by the slurry technique and loaded with Cu^{2+} (copper acetate solution). Table 1 shows examples of the separation of the enantiomers of α-amino acids[5].

The supports examined differ from each other in the type of hydrophobic spacer X that is employed. α-Amino acids with hydrophobic groups, *e.g.* Phe, Trp, Leu, Ile, Tyr, show increasing retention with increasing hydrophobic character of the spacer in the series of packings **4** > **3** > **2** > **1**. Accordingly, the retention is controlled by hydrophobic interactions. α-Amino acids with lower hydrophobicity exhibit a markedly complicated retention be-

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havior. It can be assumed that interactions by complexation, hydrophobicity or electrostatic forces take place to different extents when the hydrophobic character of the spacer changes.

Table 1. Retention values (k'_L, k'_D) and enantioselectivity coefficients ($\alpha = k'_D/k'_L$) of α-amino acids on packings **1b**—**4b**. Columns: 100×4.6 mm; column temperature 323 K; eluent: pH = 5.0; 10^{-4} M in $Cu(OAc)_2$ and 10^{-2} M in NH_4OAc; flow rate: 2 mL/min; detection: UV 254 nm. Hewlett-Packard liquid chromatograph, type 1084 A.

	1b			**2b**			**3b**			**4b**		
	k'_L	k'_D	α	k'_L	k'_D	α	k'_L	k'_D	α	k'_L	k'_D	α
Asp	1.10	1.03	0.94	2.38	2.22	0.93	2.01	2.13	1.06	16.83	16.53	0.98
Glu	1.02	1.13	1.11	1.93	2.02	1.05	1.57	1.57	1.00	12.37	14.72	1.19
His	3.80	2.33	0.61	4.13	2.48	0.60	2.22	1.92	0.86	18.50	6.53	0.35
Ala	1.40	1.47	1.05	1.33	1.60	1.20	0.40	0.58	1.45	5.50	5.70	1.04
Asn	2.05	1.76	0.86	2.52	2.35	0.93	0.89	0.82	0.92	8.58	8.28	0.97
Ser	1.72	1.46	0.85	2.12	1.67	0.79	0.82	0.74	0.92	7.36	6.25	0.85
Pro	1.93	2.51	1.30	1.93	3.15	1.63	1.07	2.06	1.93	16.43	16.33	0.99
Thr	2.14	1.94	0.91	2.78	2.32	0.83	1.14	1.16	1.02	11.73	11.50	0.98
Val	2.10	2.12	1.01	3.00	2.52	0.84	2.81	2.71	0.96	14.38	10.80	0.75
Lys	2.77	2.61	0.94	1.67	1.83	1.10	0.07	0.06	0.86	2.05	2.23	1.09
Tyr	2.30	1.52	0.66	5.85	3.67	0.63	12.25	9.72	0.79	28.58	19.73	0.69
Met	2.87	2.82	0.98	4.12	3.90	0.95	4.65	4.56	0.98	19.18	16.85	0.88
Arg	3.40	3.44	1.01	2.58	2.78	1.08	0.31	0.39	1.26	3.80	3.50	0.92
Ile	2.45	2.51	1.02	4.25	3.82	0.90	5.86	5.94	1.01	21.95	14.67	0.67
Leu	2.83	3.02	1.07	3.50	3.45	0.99	4.80	5.14	1.07	20.46	14.43	0.71
Phe	3.35	2.87	0.86	8.32	5.78	0.69	17.60	15.45	0.88	33.18	29.10	0.88
Trp	4.69	2.69	0.57	16.12	9.37	0.58	—	—	—	100.70	28.87	0.29

The supports **1**—**4** show the same sequence of elution for all α-amino acids, *i.e.* for a given amino acid the D-form appears before the L-form or *vice versa* on all phases. Exceptions are Asp, Lys, Arg, Leu, Ile. The reason for this is still unclear. With hydrophobic α-amino acids such as Thr and Tyr, containing hydroxy groups, the D-form is always eluted before the L-form. α-Amino acids with additional groups capable of complexing behave somewhat differently.

The optically active supports offer good selectivity for all α-amino acids. Mixtures of several D,L-α-amino acids can also be separated on such columns (Fig. 1).

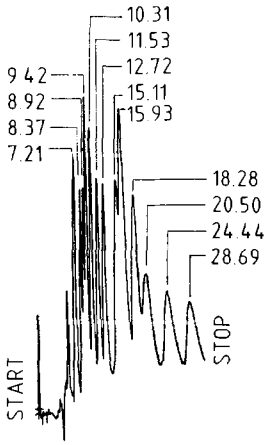

Fig. 1. Separation of unmodified α-amino acids into their enantiomers on the silica packing **2b** ($d_p = 10$ nm). Column: 250×4.2 mm; flow rate: 0.75 mL/min; column temperature: 338 K; eluent and detection, see Table 1. Elution sequence and retention times [min]: DL-Glu (7.21), L-Ala (8.37), D-Ala (8.92), D-Ser (9.42), L-Ser (10.31), D-Thr (11.53), L-Thr (12.72), D-Phe (15.11), D-His (15.93), L-Phe (18.28), D-Trp (20.50), L-His (24.44), L-Trp (28.69).

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"μ-C_3" Trisphosphanes by Direct Phosphane/Allylphosphane Coupling**

By *Ertugrul Arpac* and *Lutz Dahlenburg**

Trisphosphanes with trimethylene bridges are valuable chelating ligands for the larger transition-metal ions. Until now, the most straightforward route to this class of compounds involved lithiated trimethylenebisphosphanes, $R_2P—(CH_2)_3—P(Li)R'$ (R' = Ph, Me), which first had to be synthesized from 3-chloropropylphosphanes, $R_2P—(CH_2)_3—Cl$, and then coupled with the latter[2,3]. The range of application of the method is limited, since the key compounds $R_2P—(CH_2)_3—Cl$, which can readily be quaternized, are known only with bulky substituents on phosphorus (R = C_6H_5, *cyclo*-C_6H_{11}).

1: R = Ph; **2**: R = Me

3

Table 1. NMR data of compounds **1**, **2**, and **3** [a].

	^{31}P-NMR [b] and ^{1}H-NMR [c]	$\delta(^{31}P)$	$\delta(^1H)$	$^2J(PH)$
1	PPh_2	−17.8		
	PPh	−27.7		
	PMe_2	−54.5	0.78, 0.76	2.6, 2.7
2	PPh_2	−17.6		
	PMe	−45.0	0.77	2.7
	PMe_2	−54.2	0.83	2.7
3	PPh	−27.3		
	PMe_2	−54.5	0.78, 0.76	2.7, 2.7

	^{13}C-NMR [d]	Phenyl-C	Methylene-C	Methyl-C
1	*ipso*	137.9(14), 137.6(14)	$Me_2P—C$ 33.3(21)	Me_2P 13.5(13)
	ortho	131.8(18), 131.7(17)	$Ph_2P—C$ 29.3(21)	
	meta	127.5(7)	PhP—*C* 29.3(21)	
	para	127.7	C—*C*—C 21.9(28)	
2	*ipso*	138.4(14)	$Me_2P—C$ 33.5(22)	Me_2P 13.7(14)
	ortho	132.4(20)	MeP—*C* 31.0(25)	MeP 11.1(15)
	meta	128.1(6)	$Ph_2P—C$ 29.6(22)	
	para	128.2	C—*C*—C 21.9(27)	
3	*ipso*	138.1(16)	$Me_2P—C$ 33.4(20)	Me_2P 13.6(13)
	ortho	132.0(19)	PhP—*C* 29.5(23)	
	meta	127.9(7)	C—*C*—C 21.9(28)	
	para	128.4		

[a] Coupling parameters in Hz. [b] 36.44 MHz, toluene solutions, H_3PO_4 ext. [c] 90 and 270 MHz, C_6D_6 solutions, TMS int. [d] 22.63 MHz, $CDCl_3$ solutions, $CDCl_3$ ($\delta = 76.9$) int.; phenyl and methyl doublets with J(PC), CH_2—AB*X* triplets with $|J(P_AC) + J(P_BC)|$ in brackets.

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[**] Oligophosphane Ligands, Part 2. This work was supported by the Deutsche Forschungsgemeinschaft. *E. A.* thanks the Friedrich-Ebert-Stiftung for financial support.—Part 1: [3].

We have found that the radical addition of PH functionalized mono- and bisphosphanes to allylphosphanes offers, in principle, a more variable synthetic method, and demonstrate its efficiency by means of the one-step preparation of the two chiral ligands **1** and **2**, as well as of the derivative **3** (2 h at 110 °C in presence of 2,2'-azobis(isobutyronitrile) having permethylated terminal phosphino groups[4].

After column chromatography, **1**, **2**, and **3** were obtained in yields of *ca.* 50% as colorless oils, which were characterized by their NMR data (Table 1).

The diastereotopicity of the Me_2P fragments is clearly evident in the ^{1}H-NMR spectra of **1** and **3**: in each compound the methyl protons display two doublets with a chemical shift difference of 0.02 ppm. In **2**, in contrast, the nonequivalence of the methyl protons cannot be detected, even at 270 MHz.

Since the synthetic building blocks required for the phosphane/allylphosphane coupling are readily obtainable, we expect that using this method a series of systematically variable ligands can be prepared, by means of which the reactivity of transition-metal complexes can be controlled.

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[4] Note added in drafting the complete manuscript: *Stelzer et al.* have also synthesized a series of methylated "μ-C_3" oligophosphanes (*inter alia*, **3**) by PH/allyl-addition: M. Baacke, O. Stelzer, V. Wray, *Chem. Ber. 113* (1980) 1356; M. Baacke, S. Hietkamp, S. Morton, O. Stelzer, *ibid. 114* (1981) 2568.

Olefin Selectivities in the Addition of Carbenes**

By *Wolfgang W. Schoeller**, *Nevzat Aktekin*, and *Henniger Friege*

At variance with previous conceptions[1], according to the differential frontier model singlet carbenes can be divided into two classes depending on whether they follow a direct or inverse reactivity-selectivity relationship[2]. We have now experimentally tested this model for the electrophilic carbene series and placed it on a quantitative basis.

The following relationship applies to a change in reactivity of a carbene (C) with an olefin (O):

$$dE = \left[\frac{\partial E}{\partial \beta_{\varphi(O)\varphi(C)^*}} \frac{\partial E}{\partial \beta_{\varphi(C)\varphi(O)^*}} \frac{\partial E}{\partial E_{\varphi(O)}} \frac{\partial E}{\partial E_{\varphi(O)^*}} \frac{\partial E}{\partial E_{\varphi(C)}} \frac{\partial E}{\partial E_{\varphi(C)^*}}\right] \begin{bmatrix} d\beta_{\varphi(O)\varphi(C)^*} \\ d\beta_{\varphi(C)\varphi(O)^*} \\ dE_{\varphi(O)} \\ dE_{\varphi(O)^*} \\ dE_{\varphi(C)} \\ dE_{\varphi(C)^*} \end{bmatrix} \quad (a)$$

where E is proportional to the logarithm of the rate constant and dE corresponds to its (differential) change. From relationship (a), changes in the reactivity of a carbene (*i.e.* its selectivity), therefore result *additively* and *linearly* from changes in the individual quantities (*e.g.* orbital energies, frontier orbital coefficients, *etc.*).

With respect to (a) the following correlations were investigated: (1) π-ionization potentials of the olefins and the logarithms of the relative rate constants in addition reactions with CCl_2 [$\lg k_{rel} = a \cdot E_I(\text{olefin}) + c$] over as large a range of reactivity as possible[4] ($k_{rel} = 1$ to 1000; cf. Fig. 1); (2) *ditto* for all the carbenes studied under standard conditions[6], not only with (case a) but also without (case b) consideration of the different coefficients of the HOMO's of the various olefins [for case a) $\ln k_{rel} = a \cdot E_I(\text{olefin}) + b \cdot \text{coeff(olefin)} + c$ holds] (see Table 1). The coefficients were calculated using the CNDO/2 method.

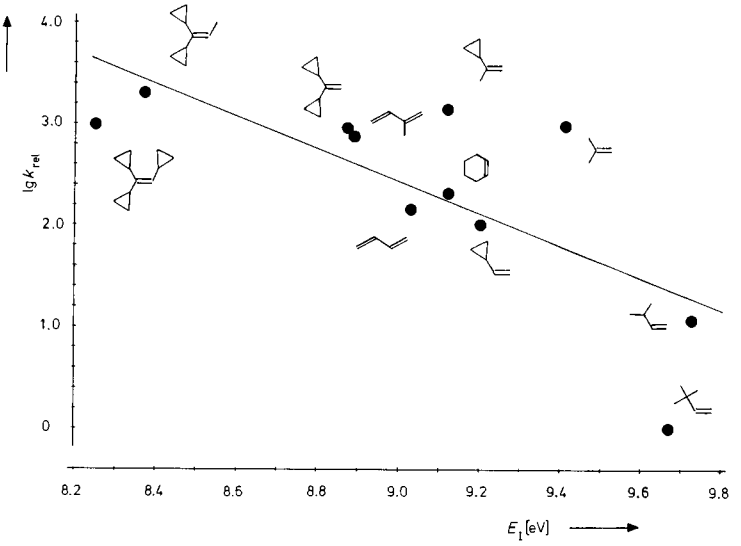

Fig. 1. Correlation of the logarithm of the relative rate constants with the π-ionization potentials of substituted olefins for the 1,2-addition of CCl_2.

As shown in Fig. 1, the relative reactivity of CCl_2 clearly increases as the π-ionization potential of the olefin decreases, however, a linear relationship is impaired by the large scattering of the points. On the other hand the correlations are greatly improved ($r^2 \approx 0.90$, case 2a) for the car-

Table 1. Parameters for the linear equation from method (2a) and relative selectivities of the carbenes ($S = a/a_{CCl_2}$) calculated from it.

Carbene	a	b	r^2	S	S_{Moss} [6]
CF_2	−8.75	36.63	0.933	1.51	1.48
CCl_2	−5.80	24.96	0.927	1.00	1.00
CBr_2	−3.70	15.80	0.887	0.64	0.65
CF^3H	−0.74	−0.12	0.945	0.13	0.12
CFCl	−7.41	30.88	0.918	1.28	1.28
CClMe	−2.82	10.08	0.872	0.49	0.50
$CBrCO_2Et$	−1.66	7.01	0.923	0.29	0.29
CClSMe	−5.51	24.28	0.961	0.95	0.93
CFPh	−5.09	22.87	0.904	0.88	0.89
CClPh	−4.67	20.96	0.850	0.81	0.83
CBrPh	−3.88	16.74	0.838	0.67	0.70
CClcPr	−2.30	9.84	0.852	0.40	0.41

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benes investigated under standard conditions, if in the parameter equation the different coefficients of the HOMO's at the various olefins are taken into consideration (Table 1).

The parameters a of the linear equations (Table 1) are a quantitative measure of the change in reactivity of a carbene with the π-ionization potential of the olefin. For CCl_2 a relative selectivity scale is obtained, which is consistent with that reported by *Moss et al.*[6]. According to differential frontier orbital theory, it is therefore possible to predict the relative reactivity of a carbene with an olefin from the corresponding linear equations. This only requires knowledge of the π-ionization potential of the olefin and the orbital coefficients of its HOMO's.

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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 (Federal Republic of Germany).

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